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RESPIRATORY SINUS ARRHYTHMIA: A POTENTIAL INDICATOR OF CHOLINERGIC TOXICOSIS IN RHESUS MONKEYS (*MACACA MULATTA*)

John A. Dellinger, Ph.D.
Heiko T. Jansen, M.S.
David J. Zaber, B.S.
Shari Birnbaum, B.S.
Bruce C. Richardson, M.S.
Gale D. Taylor, Ph.D., D.V.M.

Department of Veterinary Biosciences
University of Illinois
2001 South Lincoln Avenue
Urbana, IL 61801

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NOTICES

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The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources--National Research Council.

The Office of Public Affairs has reviewed this report, and it is releasable to the National Technical Information Service, where it will be available to the general public, including foreign nationals.

This report has been reviewed and is approved for publication.

Mark G. Swedenburg MD

MARK G. SWEDENBURG, Major, USAF, MC, SFS
Project Scientist

F. W. [illegible]

F. WESLEY BAUMGARDNER, Ph.D.
Supervisor

George Schwender MD

GEORGE E. SCHWENDER, Colonel, USAF, MC, CFS
Commander

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The vagal tone monitor (VTM) is being studied as a noninvasive tool for detecting organophosphate exposures and monitoring anticholinergic therapies. This study evaluated the VTM responses of rhesus monkeys (Macaca mulatta) after intramuscular injections of atropine sulfate, pyridostigmine bromide, physostigmine salicylate, and combinations of atropine and pyridostigmine. The VTM analyses of the electrocardiogram data yielded heart period (HP), heart period variance (HPV), and the estimate of vagal tone (V). Statistical analyses indicated that HP was more sensitive to pyridostigmine than to physostigmine, while V responded more to physostigmine and atropine than to pyridostigmine. The results also indicated that there was an attenuated response to atropine in HPV and V following pyridostigmine pretreatment. The different response of V to pyridostigmine, physostigmine, and atropine provides evidence that V is centrally rather than peripherally mediated.

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SUMMARY

The vagal tone monitor (VTM) is being studied as a tool for detecting organophosphorus (OP) exposures and monitoring anticholinergic therapies. The VTM has been used to quantify the anticholinergic effects of atropine sulfate in humans and OP-treated dogs. This study evaluated the VTM responses of rhesus monkeys (Macaca mulatta) after an anticholinergic drug (atropine sulfate), two carbamates (pyridostigmine bromide and physostigmine salicylate), and combinations of pyridostigmine and atropine. Twelve rhesus macaques were studied in four experiments using Latin square blind designs with intramuscular injections for all treatments. Experiment I tested the VTM responses to atropine sulfate injections of 0, 14, 44, and 140 µg/kg. Experiment II tested the responses to pyridostigmine injections of 0, 100, 200, and 400 µg/kg. Experiment III tested the same atropine sulfate treatments 30 min after a pyridostigmine pretreatment of 200 µg/kg. Experiment IV tested the responses to physostigmine injections of 0, 25, 50, and 100 µg/kg. The VTM analysis of the electrocardiogram data yielded heart period (HP), heart period variance (HPV), and the estimate of vagal tone (V) which were averaged over 15 min. The statistical analyses indicated that HP was more sensitive to pyridostigmine than to physostigmine, and V responded more to physostigmine and atropine than to pyridostigmine. The results also indicated that there was an attenuated atropine response following pyridostigmine pretreatment. The attenuated response had been demonstrated earlier in OP-treated dogs. The HP was primarily a measure of the peripheral cardiac responses (tachycardia vs. bradycardia), while the variance parameters contrasted the central and peripheral responses. The HPV measure provided both central and peripheral cardiac responses, while the V parameter appeared to be more centrally mediated (medullary area).

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RESPIRATORY SINUS ARRHYTHMIA: A POTENTIAL INDICATOR OF CHOLINERGIC TOXICOSIS IN RHESUS MONKEYS (MACACA MULATTA)

INTRODUCTION

Preliminary investigations using an estimate of respiratory sinus arrhythmia (RSA) have demonstrated its potential as a noninvasive measure of cholinergic function (1,2,3). Thus, RSA may prove to be a useful tool for evaluating exposure to anticholinesterase (anti-ChE) pesticides and certain nerve agents. The RSA also has potential for use in research to determine the efficacy of anticholinergics in returning cholinergic function to baseline after anti-ChE (carbamate) pretreatment. Therefore, RSA may be a useful measure of the antagonistic relationship between pretreatment carbamates (e.g., pyridostigmine) and anticholinergic therapy drugs (e.g., atropine). Therefore, the overall sensitivity of RSA to anticholinergic and anti-ChEs needed to be thoroughly investigated in an animal model.

Respiratory sinus arrhythmia was first described by Ludwig in 1847 (4) and is manifested as a decrease in the heart period (R-R interval) during inspiration and an increase in the heart period upon expiration. The amplitude of RSA is mediated by several physiological mechanisms including reflexive afferent feedback from baroreceptors (5) and volume receptors due to alterations in blood flow and intrathoracic pressure (6), afferent feedback of pulmonary stretch receptors (4), and interactions between respiratory and cardiac centers in the medulla (4,7,8,9). Pharmacologic manipulation of these neural mechanisms is expected to alter the normal pattern of nervous control to the heart.

A noninvasive measure using electrocardiographic signals and a vagal tone monitor (VTM) to estimate the vagal component of RSA was described by Porges (10). This estimate of the vagal component of RSA is based upon the occurrence of simultaneous fluctuations in heart period and respiration within a given frequency range. By separating the non-neuronal components and sympathetic activity from the heart period frequencies range, Porges et al. (11) quantified the vagal component associated with normal respiration and mathematically defined the statistic termed vagal tone (V). The VTM uses a stepwise movement of a 21-point cubic polynomial through the heart period (HP) data to calculate the variance within a 500 ms window in a frequency band of respiration of 0.12 to 0.4 Hz or 7.2 to 24 breaths per minute (human adult) or within a 2^0^0 ms window in a respiratory frequency band of 0.3 to 1.3 Hz or 18 to 78 breaths per minute (neonate human) depending on the resting respiratory rate of each monkey (32). Heart period variance and Vs are computed and analyzed with natural logarithm (ln) conversions to normalize their distributions.

Manipulations of blood pressure and heart rate (HR) have demonstrated the sensitivity of V to pharmacologic challenges. The alpha adrenergic agonist phenylephrine induced hypertension in the rabbit and was shown to increase V

through a reflex baroreceptor stimulation of the vagus (12). Vagal blockade by atropine sulfate was shown to depress V in humans (13). The peripherally acting anticholinergic atropine methylnitrate depressed V slightly in the rabbit (14). These results substantiate the hypothesis that V is an estimate of RSA. Additional experiments using anesthetic manipulation (15) and high risk neonates (16) adds further evidence to support the central nervous system (CNS) integration of RSA and the sensitivity of V to CNS brain stem function.

The ability of atropine to alleviate the signs of indirect cholinergic stimulation after anti-ChE exposure is well known. DuBois (17) first demonstrated that the acute signs of parathion-induced toxicity in laboratory animals were reversed with atropine, which indicated that the toxic effects of anti-ChE compounds are due to an indirect cholinergic overstimulation. Therapeutic doses of atropine in humans for the treatment of poisoning from anti-ChE compounds range from 2 to 4 mg intravenously (i.v.) repeated at 5- to 10-min intervals for severe cases to 1 to 2 mg/hour for less severe cases (total 25 to 50 mg/day); all treatment doses are given until signs of atropinization appear such as tachycardia, dry mouth, and flushed skin (18).

The widespread use of anti-ChE compounds may expose animals (including humans) to the potential neurotoxic consequences of both the anti-ChE and the anticholinergic treatment drugs. The successful use of atropine to protect against the toxic manifestations of these anti-ChEs is generally accepted.

Atropine's antimuscarinic actions are widespread and include effects on the peripheral and the central nervous systems. The nervous system pathway of RSA is muscarinic and, therefore, its effects on the heart can be antagonized with atropine (13,14). The specific effects of atropine sulfate on RSA were determined with doses at or below those known to affect behavior in the rhesus monkey. Penetar and McDonough (19) and McDonough (20) have shown that doses above 140 µg/kg reduce delayed match to sample performance and differential reinforcement of low rates (DRL), respectively, in the rhesus monkey.

The prescribed use of atropine at high doses for reversal of anti-ChE toxicity has been reviewed as to its potential effects on performance (13,21,22). Lobb et al. (21) concluded that the administration of atropine at protective doses (2 to 6 mg) could alter vision, alertness, equilibrium, response-force discrimination, and enunciation; information processing may also be affected. Visual discrimination performance is affected by anticholinergic compounds (23,24) by disruption of visual acuity but not color vision or the ability to discriminate colors (25). Dellinger et al. (13) compared a known alcohol-induced decrement in flight simulator performance with the effects of atropine administration. Probit analysis was used to determine an ED_{50} for atropine sulfate of 3.12 mg (42 µg/kg) with an upper 95% confidence limit of 3.88 mg (52 µg/kg), and they concluded that this concentration would be required to produce an effect comparable to a blood alcohol concentration of 0.082% in 50% of the subjects tested (13). Blood alcohol concentrations about 0.05% have been reported to cause performance decrements (26). Ketchum et al. (27) report an ED_{50} of 4.71 mg for atropine sulfate sufficient to decrease cognitive performance by 25%.

The objectives of this study were:

1. To estimate the amplitude of RSA (V) in the rhesus monkey (Macaca mulatta).

2. To examine the effects of low doses of atropine sulfate and pyridostigmine bromide (singly and in combination) on the VTM parameters of HP, overall heart period variance (HPV), and V.

3. To determine the effects of atropine on atrioventricular (A-V) conduction times as measured by the P-Q interval.

One additional objective, added to the project, was to determine the effects of physostigmine salicylate on the VTM parameters.

METHODS

Animals

Twelve juvenile to adult (4 to 9 years old) captive-born rhesus monkeys (Macaca mulatta) were used in this study. Prior to shipment to the University, all monkeys were screened for tuberculosis (TB) and had at least three negative results. Monkeys were allowed to acclimate to the housing facility for 2 weeks. Following the acclimation period, the monkeys were trained to sit quietly in a primate restraint chair. Initial restraint periods lasted 30 min and were progressively increased to 4 h. At this point normal electrocardiographic (ECG) and respiratory recordings were begun for a period of 4 weeks to establish preliminary data. For the final 2 weeks of the preliminary period, all animals were given saline placebo injections and recorded as usual.

Procedures

Experimental Designs

Experiment I. (Atropine). Data were recorded from all 12 monkeys. A Latin square blind design was used to assign doses (Table 1). Each monkey's assignment to groups (rows) and treatment sequence (columns) was randomized. All responses to atropine sulfate and the saline placebo were recorded. Groups consisted of 3 animals with each group receiving a different dose sequence. Each monkey received doses of 0, 14, 44, and 140 µg of atropine sulfate per kg of body weight. Intramuscular (i.m.) injections were made into the right lateral aspect of the calf.

TABLE 1. ATROPINE SULFATE TREATMENTS USED IN THE LATIN SQUARE DESIGN[a]

Group[b]	Recording session A	B	C	D
1	0	44	140	14
2	140	14	0	44
3	14	0	44	140
4	44	140	14	0

[a]Treatments expressed as µg of Atropine Sulfate per kg of body weight.
[b]Three animals per treatment group.

Each atropine sulfate dose was administered according to the animal's actual weight. Experimental sessions were separated by 1 week. Atropine sulfate[1] (stock concentration = 15 mg/cm^3) was prepared weekly in isotonic saline. Calculated doses were administered in a final volume 0.1 cm^3/kg. Blood was collected for ChE determinations in ethylenediaminetetraacetate (EDTA) tubes by cephalic venipuncture during the 30-min baseline period.

Experiment II. (Pyridostigmine). Similar to Experiment I, data were recorded from the same 12 monkeys. A Latin square blind design was used to assign doses (Table 2). Each animal's assignment to group (rows) and treatment sequence (columns) was randomized. Prior to the treatments, each animal completed 1 week of acclimation to the experimental procedures and 1 week of baseline recording complete with saline injections. All responses to pyridostigmine bromide and the saline placebo were recorded.

TABLE 2. PYRIDOSTIGMINE BROMIDE TREATMENTS [a] USED IN THE LATIN SQUARE DESIGN

Group[b]	Recording session A	B	C	D
1	400	0	100	200
2	200	400	0	100
3	0	100	200	400
4	100	200	400	0

[a]Treatments expressed as µg Pyridostigmine Bromide per kg of body weight.
[b]Three animals per treatment group.

[1]Med-Tech Inc., Elwood, Kansas. 15 mg/ml, Lot 5080C, Exp 3/88.

Groups consisted of three animals with each group receiving a different dose sequence. All animals received doses of 0, 100, 200, and 400 μg of pyridostigmine bromide per kg of body weight. Intramuscular injections were made into the right lateral aspect of the calf. Each pyridostigmine dose was administered according to the animal's actual weight. The injections were separated by 1 week. Pyridostigmine bromide[2] (stock concentration = 5 mg/cm^3) was prepared weekly in isotonic saline. Calculated doses were administered in a final volume of 0.1 cm^3/kg.

Blood was collected for ChE determinations in EDTA tubes by cephalic venipuncture. Three blood samples were collected from each individual: (1) after a 30-min baseline period, (2) 30 min after pyridostigmine, and (3) 180 min after dosing. Cholinesterase assays were always completed within 1 h of collection to minimize spontaneous reactivation.

Experiment III. (Pyridostigmine + Atropine). Similar to Experiments I and II, data were recorded from the same 12 monkeys. However, in this experiment, all monkeys received a 200 μg pyridostigmine pretreatment 30 min before each atropine injection. A Latin square blind design was used to assign atropine doses (Table 3) to the four groups. Each monkey's assignment to groups (rows) and treatment sequence (columns) was randomized. Because of an error in dosing during the first week, groups consisted of 3 animals in 2 of the groups, 2 animals in one group, and 4 animals in the last group. Before treatments, each monkey completed 1 week of acclimation to the experimental procedures and 1 week of baseline recording complete with saline injections. All responses to pyridostigmine bromide and atropine or the saline placebo were recorded. Each monkey received doses of 0, 14, 44, and 140 μg of atropine sulfate per kg of body weight 30 min after the 200 μg/kg pyridostigmine pretreatment. The atropine sulfate (stock concentration = 15 mg/cm^3) was prepared in isotonic saline and drawn weekly for individual doses. Pyridostigmine bromide (stock concentration = 5 mg/cm^3) was prepared in isotonic saline and drawn daily from this preparation. Intramuscular injections were made into the lateral aspect of the right calf and the treatments were administered according to the animal's actual weight with a final volume of 0.1 cm^3/kg body weight.

Blood was collected for ChE determinations in EDTA tubes by cephalic venipuncture. Three blood samples were collected from each individual: once before the 30-min baseline period, and at 30 and 180 min after pyridostigmine dosing. Cholinesterase assays were always completed within 1 h of collection to minimize spontaneous reactivation.

Experiment IV. (Physostigmine). Similar to Experiment I, data were recorded from the same 12 monkeys. A Latin square blind design was used to assign doses (Table 4). Each monkey's assignment to groups (rows) and treatment sequence (columns) was randomized. Before treatments, each monkey completed 1 week of acclimation to the experimental procedures and 1 week of

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[2]Roche Laboratories, Nutley, NJ. 10 mg/5 ml, Lot 0103, Exp. 8/87.

baseline recording complete with saline injections. All responses to physostigmine salicylate and the saline placebo were recorded. Groups consisted of three animals with each group receiving a different dose sequence. Each monkey received doses of 0, 25, 50, and 100 µg of physostigmine salicylate per kg of body weight. Intramuscular injections were made into the right lateral aspect of the calf. Each physostigmine dose was administered according to the animal's actual weight. Injections were separated by 1 week. Physostigmine salicylate[3] (stock concentration = 1 mg/cm^3) was prepared weekly in isotonic saline. Calculated doses were administered in a final volume of 0.1 cm^3/kg.

Blood was collected for ChE determinations in EDTA tubes by cephalic venipuncture. Three blood samples were collected from each individual once during a 30-min baseline period and at 30 and 180 min after physostigmine dosing. Cholinesterase assays were always completed within 1 h of collection to minimize spontaneous reactivation.

TABLE 3. ATROPINE SULFATE TREATMENTS USED IN THE LATIN SQUARE DESIGN[a] 30 MIN FOLLOWING 200 µg PYRIDOSTIGMINE BROMIDE PER KILOGRAM BODY WEIGHT

	Recording session			
Group	A	B	C	D
1[b]	44	140	0	14
2[c]	14	44	140	0
3[b]	0	14	44	140
4[d]	140	0	14	44

[a]Treatments expressed as µg of atropine sulfate per kg body weight.
[b]Three animals per group.
[c]Two animals per group.
[d]Four animals per group.

TABLE 4. PHYSOSTIGMINE SALICYLATE TREATMENTS[a] USED IN THE LATIN SQUARE DESIGN

	Recording session			
Group[b]	A	B	C	D
1	50	0	25	100
2	25	100	0	50
3	0	50	100	25
4	100	25	50	0

[a]Treatments expressed as µg physostigmine salicylate per kg of body weight.
[b]Three animals per treatment group.

[3]Forest Pharmaceuticals Inc., St. Louis, MO. 1 mg/ml, Lot 85F096, Exp. 10/89.

Equipment and Analyses

Physiological Data Recordings

Data were collected from each monkey while seated in a sound-attenuating chamber. A standard Lead II ECG configuration was used for the determination of heart rate and to estimate the activity of the vagus on the A-V node by measuring the P-Q interval. Data were transmitted to a physiograph[4] and recorded on heat-sensitive paper. Respiratory data were collected using a bellows/pressure transducer apparatus[5] and recorded on paper for respiratory frequency determinations.

All ECG signals were passed through a two-channel oscilloscope for verification and amplification (if required). Electrocardiographic signals were transmitted to a 4-channel cassette recorder[6] and a VTM[7] for continuous recording and real-time analyses, respectively. Respiratory data were transmitted to the recorder and stored on cassette tape along with the ECG data.

After the data were collected for Experiment I, an examination of the respiratory data for each monkey indicated that 6 of the 12 animals normally respired within the adult human frequency range of .12 to .40 Hz and 6 within the human neonate frequency of .3 to 1.3 Hz. Therefore, for all four experiments, the 12 monkeys were divided into a "neonatal human" or "adult human" group with regard to the respiratory settings on the VTM.

Electrocardiographic and respiratory data were recorded on paper every 15 min during the 30-min baseline interval. After dosing, data were recorded every 5 min for the first 30 min and subsequently every 15 min for the duration of the 3-h experimental session.

Cholinesterase Activity Determination

Cholinesterase activity was determined using a modification of the colorimetric method of Ellman et al. (28). Plasma and erythrocytes were separated following centrifugation at 2000 x G for 10 min. Erythrocytes were washed immediately with an equal volume of ice-cold isotonic saline and recentrifuged (Experiment I only). The supernatant was discarded and the erythrocyte wash repeated twice. For the carbamate experiments (II, III, and IV), the erythrocytes were not washed because washing can remove the carbamate which is not bound to the enzyme and allows more time for spontaneous reactivation (29). Erythrocytes (0.1 ml) were hemolyzed with 1.9 ml of a 5% Triton-X solution. A 0.5 ml aliquot of the lysed solution was diluted to 25 ml with 0.1 M phosphate buffer, pH 8.0 for erythrocyte assays (Experiment I only). For Experiments II, III, and IV, 1 ml of the erythrocyte dilution was added to an additional 2 ml of 0.1 M phosphate

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[4]Gilson Medical Electronics, Middleton, WI.
[5]Gould Inc., Oxnard, CA.
[6]A. R. Vetter Co., Rebersberg, PA.
[7]Delta Biometrics, Bethesda, MD.

buffer, pH 8.0. A 0.01-ml sample of plasma was diluted 10 ml with 0.1 M phosphate buffer, pH 8.0 for plasma determinations.

Activity was determined in 3.0-ml volumes of the phosphate buffered samples. Dithiobis (nitrobenzoic acid) (DTNB; 0.01 M, 0.05 ml) was added to the buffered sample. Substrate, 0.075 M acetylthiocholine iodide (ATCI; 0.02 ml) was added to the sample and the absorbance changes at 412 nm monitored for 5 min at approximately 20°C (68°F) on an SLM-Aminco DW-2^{r}C[8] spectrophotometer and a Midan^{r}II kinetic processor/integrator (Experiment I). A Beckman DU-5 spectrophotometer[9] was used for Experiments II, III, and IV. The absorbance changes at 412 nm on the Beckman DU-5 spectrophotometer were monitored for 3 min. The reagents for the assay were prepared weekly. Human serum standards[10] were analyzed daily. Data are reported as millimole of acetylthiocholine iodide hydrolyzed/liter/minute.

Data Analysis

The ECG signals recorded during each experimental session were digitized using the VTM and the data transmitted to a computer for storage on floppy diskettes. These signals were used to calculate mean HR, mean HP, and mean HPV during 15-min intervals. The VTM digitizes the ECG signal, determines the R-wave, measures the R-R interval in ms (HP), and computes HPV.

The HP information was then converted to time-based sequences (500 ms windows for the 0.12 to 0.4 Hz respiratory band and 200 ms for the 0.3 to 1.3 Hz respiratory band), and then a 21-point cubic polynomial was used as a high-pass filter with a low-frequency cutoff to determine V as the HP variance within the normal respiratory band (15,30). Natural logarithms (ln) were used for normalizing the distributions of the two variance measures, HPV and V.

Estimates of each measure were computed every 30 s. Fifteen minutes of data for each variable (HR, HP, HPV, and V) were summarized as mean HR beats per minute (bpm), mean HP (ms), mean HPV (ln ms^2), and mean V (ln ms^2) and used in the statistical analysis.

Statistical Analysis

A general linear model (GLM) procedure[11] was used to perform a univariate analysis of variance (ANOVA) to test the main effects (animal [nested within group], group, week, time, dose) and the interactions of these main effects. The GLM corresponds to a split-plot repeated measures design (31). Individual variability was expected and produced a large F-statistic that was corrected for in the overall statistical model by partitioning of the

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[8]SLM Instruments, Inc., American Instruments Co., Urbana, IL.
[9]Beckman Model 45, Beckman Instruments Inc., Irvine, CA.
[10]Sera Chem., Clinical Chemistry Control, Fisher Diagnostics, Organgeburg, NY.
[11]SAS Institute Inc., Cary, NC.

appropriate error term. The F-ratios and probabilities for all the main effects and the interactions tested are reported in the Appendixes A, B, C, F, G, H, K, L, M, P, Q, and R. Summaries of these appendixes are provided as tables in the Results section (Tables 5, 10, 15, and 20). Similar ANOVAs were performed to test the ChE and P-Q interval data. Differences within the main effects were further analyzed using a Tukey's Studentized Range Test[12] for comparison of overall means and are reported in the Results section.

Probit analysis[12] was used for computing ED_{50}s for a 30% decrease (atropine and pyrido/atropine) in HPV and V to allow for comparisons to earlier work by Dellinger et al. (13) and to determine the relative sensitivity of each parameter. Throughout this study, ED_{50} values reflect a 30% decrease in the parameter measured. Chi-square values were used to describe the "goodness of fit" of the probit line to the data. A small chi-square ($p > .10$) indicated a good fit (i.e., the probit line approximated the data).

All significance testing used an alpha level of 0.05. The default SAS Probit Analysis[12] alpha ($p > .10$) was used for the chi-square testing of estimated probit lines.

RESULTS

Experiment I (Atropine Sulfate)

Vagal Tone Monitoring

The four variables tested (HR, HP, HPV, and V) differed in their responses to atropine sulfate (Figs. 1-3, HR not shown; Tables 5-9; Appendixes A and B). A significant increase in the HR was observed at both 30 and 45 min at 44 and 140 µg/kg atropine (Table 6). Heart rate exhibited a significant dose effect and dose*time interaction. Heart period (Fig. 1) was significantly decreased at the 44 and 140 µg/kg doses at 45 min (Table 7). A significant dose*time interaction was observed, yet dose alone was not significant. Heart period variance (Fig. 2; Table 8) and V (Fig. 3; Table 9) were significantly decreased at the high dose of atropine between 15 and 180 min. Heart period variance exhibited significant dose*time and dose effects. The estimate of RSA amplitude (V) exhibited only dose effect.

Heart period variance exhibited a dose-response relationship after dosing with atropine. The estimate of RSA (V) fell to near zero and, therefore, did not differentiate the middle and high doses clearly. The significant dose*time effects were analyzed by a Tukey's Studentized Range test. The results indicated that the mean HPV for the placebo was greater than for all doses. Contrasts between responses at each dose indicated that all comparisons produced significant differences at 45 min except between the middle and high dose. For the estimate of RSA (V), the placebo level of V was greater than at all doses, but these did not differ from one another. Figure 4 represents the overall means for the four dose levels and the mean peak response at 45 min for HPV and V.

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[12]Beckman Model 45, Beckman Instruments Inc., Irvine, CA.

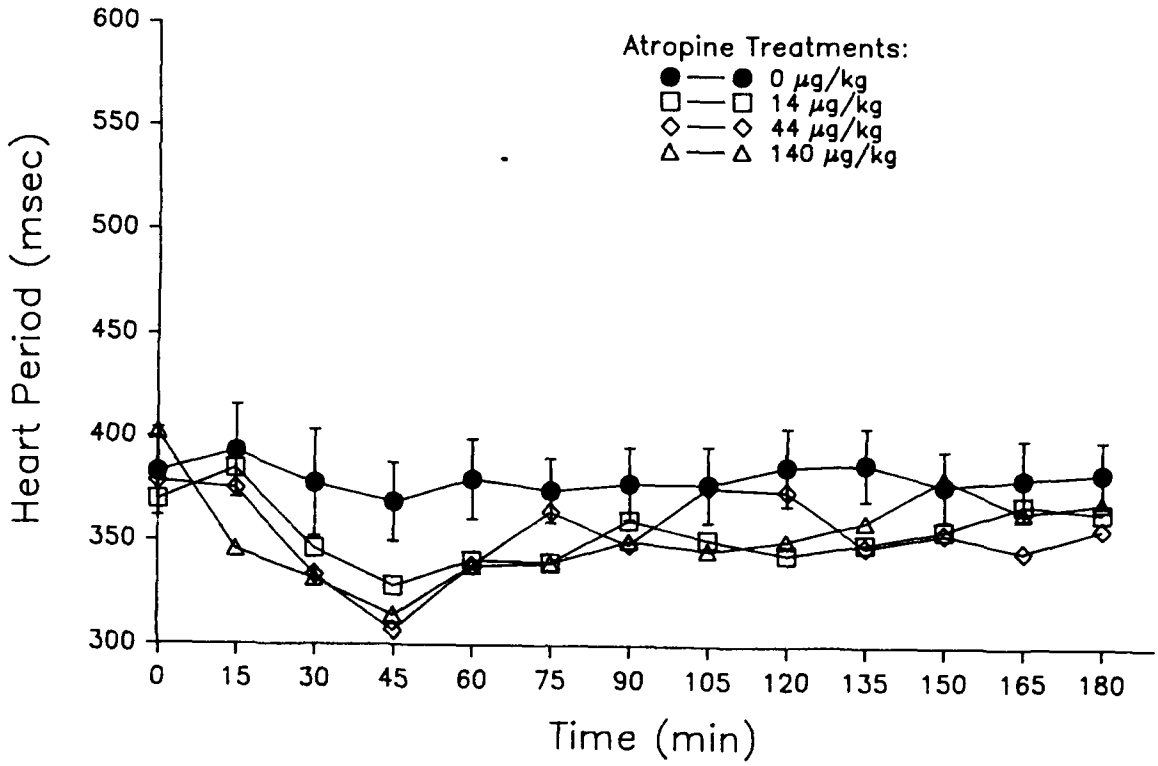

Figure 1. Mean heart period responses vs. time for 4 atropine sulfate treatment conditions (n = 12).

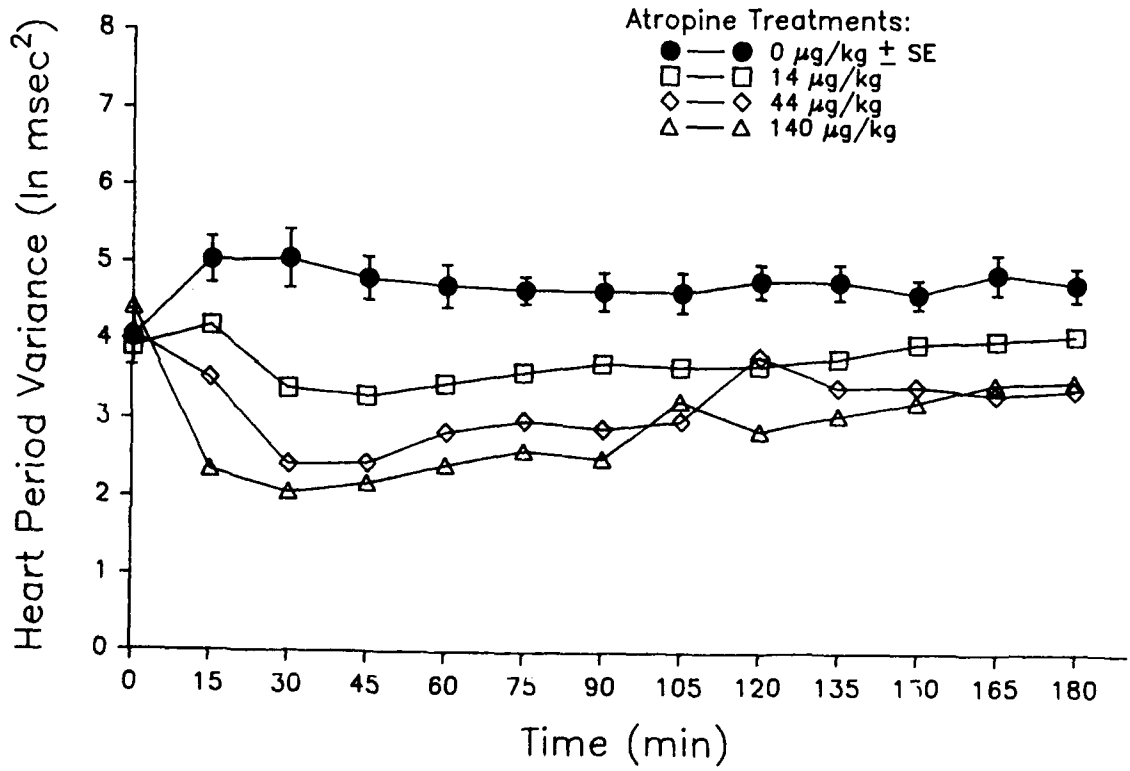

Figure 2. Mean heart period variance responses vs. time for 4 atropine sulfate treatment conditions (n = 12).

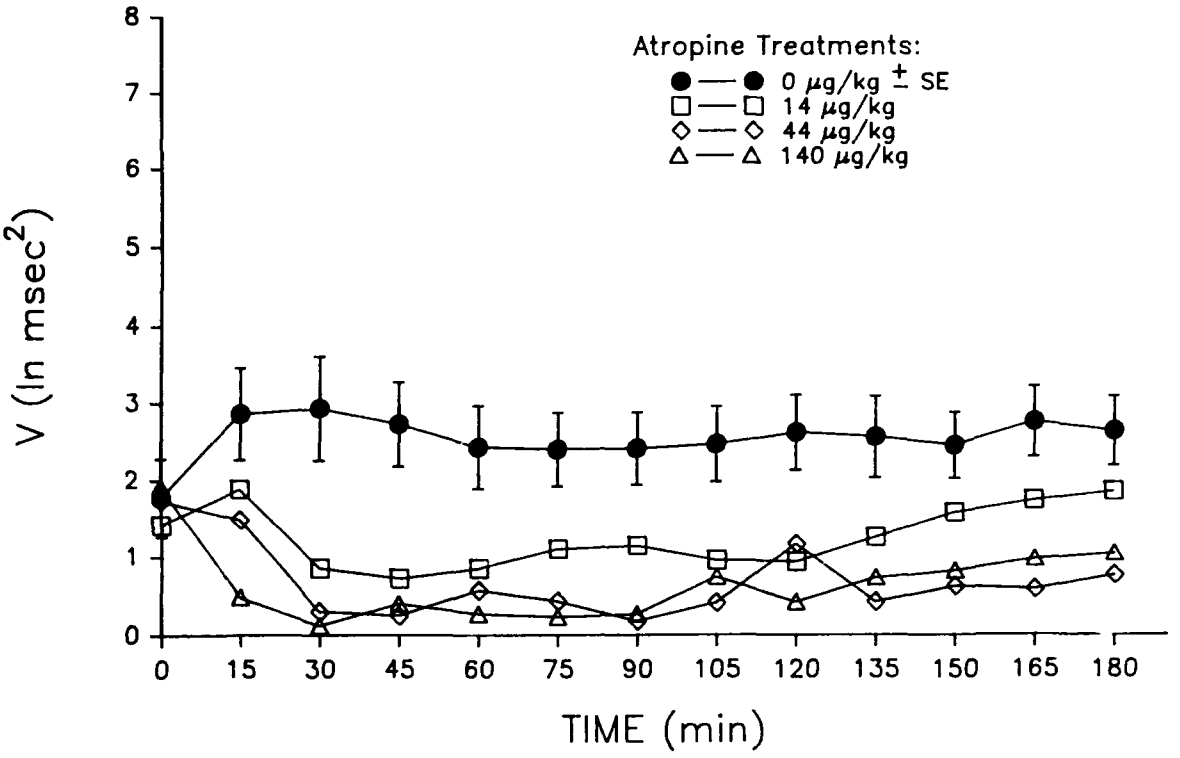

Figure 3. Mean estimate of respiratory sinus arrhythmia amplitude (V) responses vs. time for 4 atropine sulfate treatment conditions (n = 12).

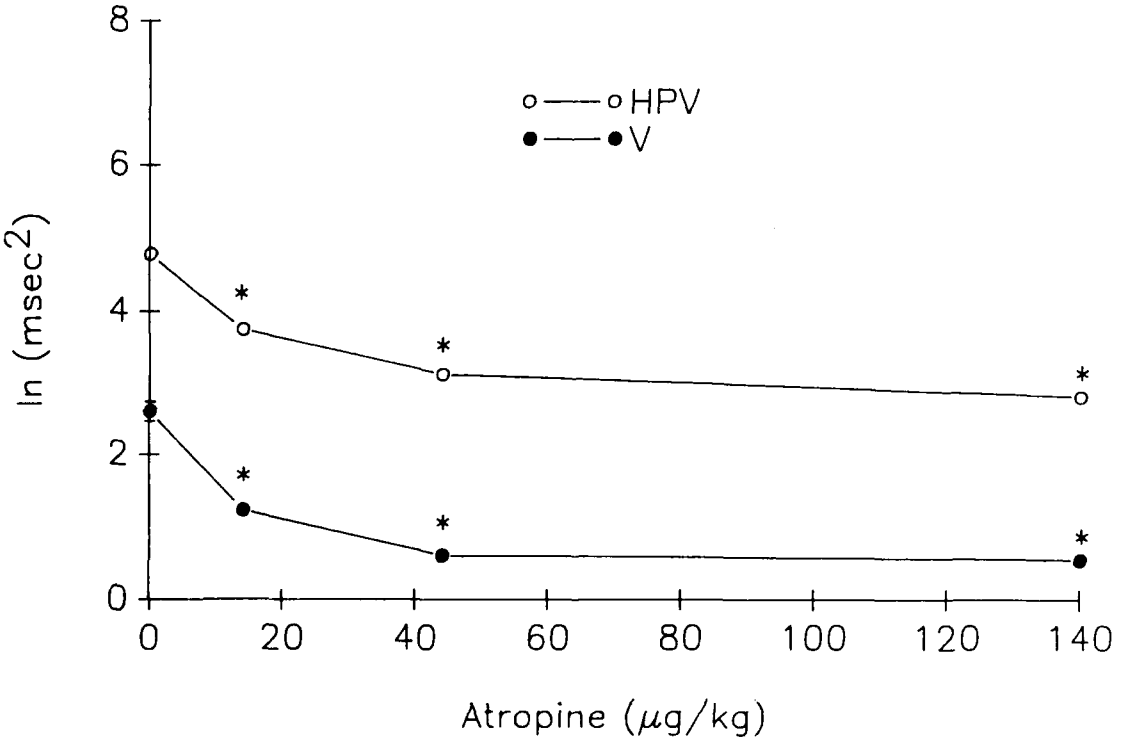

Figure 4. Mean heart period variance and estimated respiratory sinus arrhythmia amplitude (V) responses for 4 atropine sulfate treatment conditions (n = 12).

TABLE 5. F-RATIOS AND PROBABILITIES FOR MAIN AND INTERACTIVE EFFECTS AFTER ATROPINE IN THE RHESUS MONKEY

Dependent variable	F-ratios		
	Dose*time	Dose	Time
HR	1.82 P < .005	2.91 P < .055	4.30 P < .0001
HP	1.23 P < .186	1.18 P < .156	3.97 P < .0001
HPV	1.86 P < .004	25.23 P < .0001	5.45 P < .0001
V	1.43 P < .069	14.20 P < .0001	2.94 P < .002
			Week
Erythrocyte ChE	--	--	0.61 P < .617
Plasma ChE	--	--	1.90 P < .154

TABLE 6. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR HEART RATE

Trt. contrast (µg/kg)	Time after atropine sulfate injection (min)					
	15	30	45	60	75	90
0 to 14	NS	*	NS	NS	NS	NS
0 to 44	NS	*	*	NS	NS	NS
0 to 140	NS	*	*	NS	NS	NS
14 to 44	NS	NS	NS	NS	NS	NS
14 to 140	NS	NS	NS	NS	NS	NS
44 to 140	NS	NS	NS	NS	NS	NS

Trt. contrast (µg/kg)	Time after atropine sulfate injection (min)					
	105	120	135	150	165	180
0 to 14	NS	NS	NS	NS	NS	NS
0 to 44	NS	NS	NS	NS	NS	NS
0 to 140	NS	NS	NS	NS	NS	NS
14 to 44	NS	NS	NS	NS	NS	NS
14 to 140	NS	NS	NS	NS	NS	NS
44 to 140	NS	NS	NS	NS	NS	NS

*Contrast is significant, p < .05.

TABLE 7. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR HEART PERIOD

Trt. contrast (µg/kg)	Time after atropine sulfate injection (min)					
	15	30	45	60	75	90
0 to 14	NS	NS	NS	NS	NS	NS
0 to 44	NS	NS	*	NS	NS	NS
0 to 140	NS	NS	*	NS	NS	NS
14 to 44	NS	NS	NS	NS	NS	NS
14 to 140	NS	NS	NS	NS	NS	NS
44 to 140	NS	NS	NS	NS	NS	NS

Trt. contrast (µg/kg)	Time after atropine sulfate injection (min)					
	105	120	135	150	165	180
0 to 14	NS	NS	NS	NS	NS	NS
0 to 44	NS	NS	NS	NS	NS	NS
0 to 140	NS	NS	NS	NS	NS	NS
14 to 44	NS	NS	NS	NS	NS	NS
14 to 140	NS	NS	NS	NS	NS	NS
44 to 140	NS	NS	NS	NS	NS	NS

*Contrast is significant, $p < .05$.

TABLE 8. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR HEART PERIOD VARIANCE

Trt. contrast (µg/kg)	Time after atropine sulfate injection (min)					
	15	30	45	60	75	90
0 to 14	NS	*	*	*	*	NS
0 to 44	*	*	*	*	*	*
0 to 140	*	*	*	*	*	*
14 to 44	NS	NS	*	NS	NS	NS
14 to 140	*	*	*	NS	NS	*
44 to 140	NS	NS	NS	NS	NS	NS

Trt. contrast (µg/kg)	Time after atropine sulfate injection (min)					
	105	120	135	150	165	180
0 to 14	NS	NS	*	NS	NS	NS
0 to 44	*	NS	*	*	*	*
0 to 140	*	*	*	*	*	*
14 to 44	NS	NS	NS	NS	NS	NS
14 to 140	NS	NS	NS	NS	NS	NS
44 to 140	NS	NS	NS	NS	NS	NS

*Contrast is significant, $p < .05$.

TABLE 9. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR VAGAL TONE

Trt. contrast (µg/kg)	Time after atropine sulfate injection (min)					
	15	30	45	60	75	90
0 to 14	NS	*	*	*	*	*
0 to 44	NS	*	*	*	*	*
0 to 140	*	*	*	*	*	*
14 to 44	NS	NS	NS	NS	NS	NS
14 to 140	*	NS	NS	NS	NS	NS
44 to 140	NS	NS	NS	NS	NS	NS

Trt. contrast (µg/kg)	Time after atropine sulfate injection (min)					
	105	120	135	150	165	180
0 to 14	*	*	*	NS	*	NS
0 to 44	*	NS	*	*	*	*
0 to 140	*	*	*	*	*	*
14 to 44	NS	NS	NS	NS	*	*
14 to 140	NS	NS	NS	NS	*	NS
44 to 140	NS	NS	NS	NS	NS	NS

*Contrast is significant, $p < .05$.

P-Q Intervals. Conduction times at the A-V node were significantly decreased at all doses when compared to the placebo 150 min after injection (Table 10; Appendix C). The 14 µg/kg dose and the placebo produced a transient increase in the P-Q interval between 0 and 15 min which correlated with a bradycardia during the same interval followed by the tachycardia.

Cardiology. Examination of the ECG data revealed that one monkey exhibited a persistent pattern of premature ventricular beats which appeared to increase after the low dose of atropine. Another monkey occasionally exhibited S-A nodal block but this was not seen after atropine. Junctional premature beats were observed in one monkey but did not change in frequency after atropine. The amplitude of the P-wave was frequently observed to fluctuate and in one case reversed its polarity after atropine, possibly due to the unmasking of a neuroeffector site originating in the left atrium and innervated by the vagus (32). No signs of A-V dissociation or heart block after atropine, as sometimes seen in the human (33,34), were observed.

Cholinesterase. Plasma ChE activity varied significantly between monkeys as did erythrocyte activity (Appendix D). No significant changes in activity during the 4-week preliminary period for either activity were observed.

Plasma and erythrocyte ChE activity was determined for the 4-week preliminary period for each animal. The overall means for plasma and erythrocyte ChE activity were 2.04 and 5.00 mM/L/min, respectively

(Appendixes E and F). These values are similar to those of the human (serum: 1.88-3.13 mM/L/min and erythrocyte: 3.00-5.00 mM/L/min; Bio-Dynamics/bmc, 1977).

Probit Analyses. The ED_{50}s for HPV and V were determined from the VTM data. A 30% decrease in HPV and V was used for comparison to earlier work by Dellinger et al. (13). The number of animals that responded at each dose was used to estimate the ED_{50}. The ED_{50} for HPV was estimated to be 29 µg/kg (χ^2 [1, $\underline{N}$ = 2] = 0.0137, $p > 0.9068$) and for V was estimated to be 9 µg/kg (χ^2 [1, $\underline{N}$ = 2] = 0.1051, $p > 0.7458$). The estimate of RSA (V) was determined to be more sensitive to the anticholinergic effects of atropine sulfate than HPV (also compare Figs. 2 and 3 at the low dose).

Frequency Spectrum Plot. Dr. Stephen Porges analyzed samples of the rhesus ECG tapes using spectral density analysis on a DEC PDP-11 computer. Figure 5 shows the results of one of the analyses. The analysis confirms the presence of a large slow wave component in the monkey which is present at 0.08 Hz and is distinct from the respiratory-heart period frequencies. This pattern is representative of the other monkeys. Human slow wave and V activity have been reported to occur within similar frequencies, but with less slow wave activity and more V activity (35,36).

Experiment II (Pyridostigmine Bromide)

Vagal Tone Monitoring

Figures 6, 7, and 8 illustrate the VTM parameter responses (HP, HPV, and V) to pyridostigmine bromide for the 12 monkeys. Table 11 summarizes the ANOVA results of Appendix F. Appendix G lists raw data. Tables 12, 13, 14, and 15 provide the Tukey's contrast testing for each data point for HR, HP, HPV, and V, respectively.

Three of the four variables tested (HR [not shown], HP, and HPV) produced statistically significant dose effects (Table 11). The V response was not significant for treatment; however, there was a significant dose*time interaction for both HP and V. The other parameters measured did not display a significant effect for the dose*time interaction. There was a significant time effect for all parameters measured after exposure to pyridostigmine bromide.

There was a significant dose effect for HR and HP at 30 and 45 min. According to the Tukey's contrast (Tables 12 and 13), the significant decrease in HR and increase in HP was due mainly to the difference between the high (400 µg) dose and the placebo control.

There was a significant difference between the mid (200 µg) dose and control response for HPV at 45 min (Table 14). A significant increase in HPV also occurred at 165 min between the control and high (400 µg) dose response. In addition, a significant difference between the high (400 µg) and low (100 µg) dose occurred at 105, 150, and 180 min.

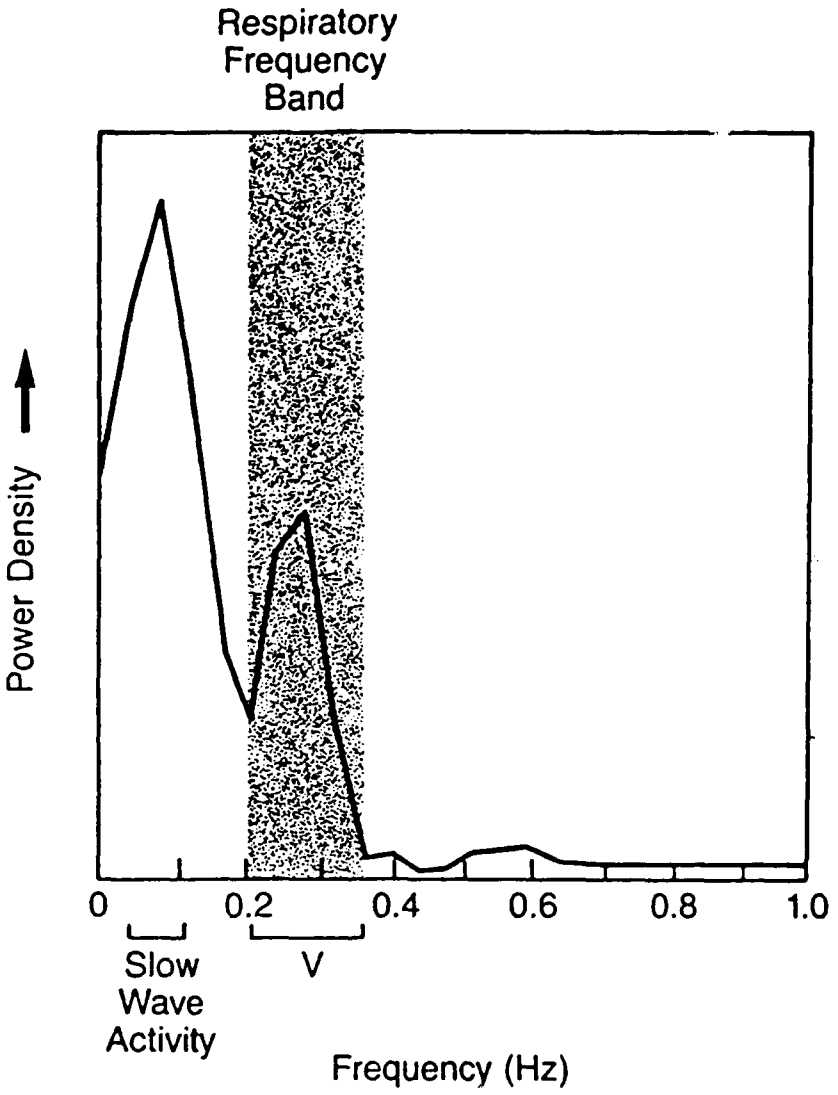

Figure 5. Frequency spectrum plot of rhesus heart period (Animal #N597). Regions of slow wave activity and estimated amplitude of respiratory sinus arrhythmia are shown.

TABLE 10. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR P-Q INTERVALS

Trt. contrast (μg/kg)	Time after atropine sulfate injection (min)					
	15	30	45	60	75	90
0 to 14	NS	NS	NS	NS	NS	NS
0 to 44	NS	NS	NS	NS	NS	*
0 to 140	NS	NS	NS	NS	NS	NS
14 to 44	NS	NS	NS	NS	NS	NS
14 to 140	NS	NS	NS	NS	NS	NS
44 to 140	NS	NS	NS	NS	NS	NS

Trt. contrast (μg/kg)	Time after atropine sulfate injection (min)					
	105	120	135	150	165	180
0 to 14	NS	NS	NS	*	NS	NS
0 to 44	*	NS	NS	*	NS	NS
0 to 140	NS	NS	*	*	NS	*
14 to 44	NS	NS	NS	NS	NS	NS
14 to 140	NS	NS	NS	NS	NS	NS
44 to 140	NS	NS	NS	NS	NS	NS

*Contrast is significant, $p < .05$.

TABLE 11. F-RATIOS AND PROBABILITIES FOR MAIN AND INTERACTIVE EFFECTS AFTER PYRIDOSTIGMINE IN THE RHESUS MONKEY

Dependent variable	F-ratios		
	Dose*time	Dose	Time
HR	0.57 P < .971	4.01 P < .019	10.22 P < .0001
HP	0.53 P < .0001	5.30 P < .006	7.37 P < .0001
HPV	0.84 P < .718	9.03 P < .0003	6.06 P < .0001
V	1.49 P < .048	2.45 P < .089	3.37 P < .0006
Erythrocyte ChE	17.24 P < .0001	57.74 P < .0001	87.98 P < .0001
Plasma ChE	19.41 P < .0001	49.08 P < .0001	35.07 P < .0001

TABLE 12. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR HEART RATE

Trt. contrast (μg/kg)	Time after pyridostigmine bromide injection					
	15	30	45	60	75	90
0 to 100	NS	NS	NS	NS	NS	NS
0 to 200	NS	NS	NS	NS	NS	NS
0 to 400	NS	*	*	NS	NS	NS
100 to 200	NS	NS	NS	NS	NS	NS
100 to 400	NS	NS	NS	NS	NS	NS
200 to 400	NS	NS	NS	NS	NS	NS

Trt. contrast (μg/kg)	Time after pyridostigmine bromide injection					
	105	120	135	150	165	180
0 to 100	NS	NS	NS	NS	NS	NS
0 to 200	NS	NS	NS	NS	NS	NS
0 to 400	NS	NS	NS	NS	NS	NS
100 to 200	NS	NS	NS	NS	NS	NS
100 to 400	NS	NS	NS	NS	NS	NS
200 to 400	NS	NS	NS	NS	NS	NS

*Contrast is significant, $p < 0.05$.

TABLE 13. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR HEART PERIOD

Trt. contrast (μg/kg)	Time after pyridostigmine bromide injection					
	15	30	45	60	75	90
0 to 100	NS	NS	NS	NS	NS	NS
0 to 200	NS	NS	NS	NS	NS	NS
0 to 400	NS	*	*	NS	NS	NS
100 to 200	NS	NS	NS	NS	NS	NS
100 to 400	NS	NS	NS	NS	NS	NS
200 to 400	NS	NS	NS	NS	NS	NS

Trt. contrast (μg/kg)	Time after pyridostigmine bromide injection					
	105	120	135	150	165	180
0 to 100	NS	NS	NS	NS	NS	NS
0 to 200	NS	NS	NS	NS	NS	NS
0 to 400	NS	NS	NS	NS	NS	NS
100 to 200	NS	NS	NS	NS	NS	NS
100 to 400	NS	NS	NS	NS	NS	NS
200 to 400	NS	NS	NS	NS	NS	NS

*Contrast is significant, $p < 0.05$.

TABLE 14. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR HEART PERIOD VARIANCE

Trt. contrast (μg/kg)	Time after pyridostigmine bromide injection					
	15	30	45	60	75	90
0 to 100	NS	NS	NS	NS	NS	NS
0 to 200	NS	NS	*	NS	NS	NS
0 to 400	NS	NS	NS	NS	NS	NS
100 to 200	NS	NS	NS	NS	NS	NS
100 to 400	NS	NS	NS	NS	NS	NS
200 to 400	NS	NS	NS	NS	NS	NS

Trt. contrast (μg/kg)	Time after pyridostigmine bromide injection					
	105	120	135	150	165	180
0 to 100	NS	NS	NS	NS	NS	NS
0 to 200	NS	NS	NS	NS	NS	NS
0 to 400	NS	NS	NS	NS	*	NS
100 to 200	NS	NS	NS	NS	NS	NS
100 to 400	*	NS	NS	*	NS	*
200 to 400	NS	NS	NS	NS	NS	NS

*Contrast is significant, $p < 0.05$.

TABLE 15. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR VAGAL TONE

Trt. contrast (μg/kg)	Time after pyridostigmine bromide injection					
	15	30	45	60	75	90
0 to 100	NS	NS	NS	NS	NS	NS
0 to 200	NS	NS	NS	NS	NS	NS
0 to 400	NS	NS	NS	NS	NS	NS
100 to 200	NS	NS	NS	NS	NS	NS
100 to 400	NS	NS	NS	NS	NS	NS
200 to 400	NS	NS	NS	NS	NS	NS

Trt. contrast (μg/kg)	Time after pyridostigmine bromide injection					
	105	120	135	150	165	180
0 to 100	NS	NS	NS	NS	NS	NS
0 to 200	NS	NS	NS	NS	NS	NS
0 to 400	NS	NS	NS	NS	*	NS
100 to 200	NS	NS	NS	NS	NS	NS
100 to 400	NS	NS	*	NS	NS	NS
200 to 400	NS	NS	NS	NS	NS	NS

*Contrast is significant, $p < 0.05$.

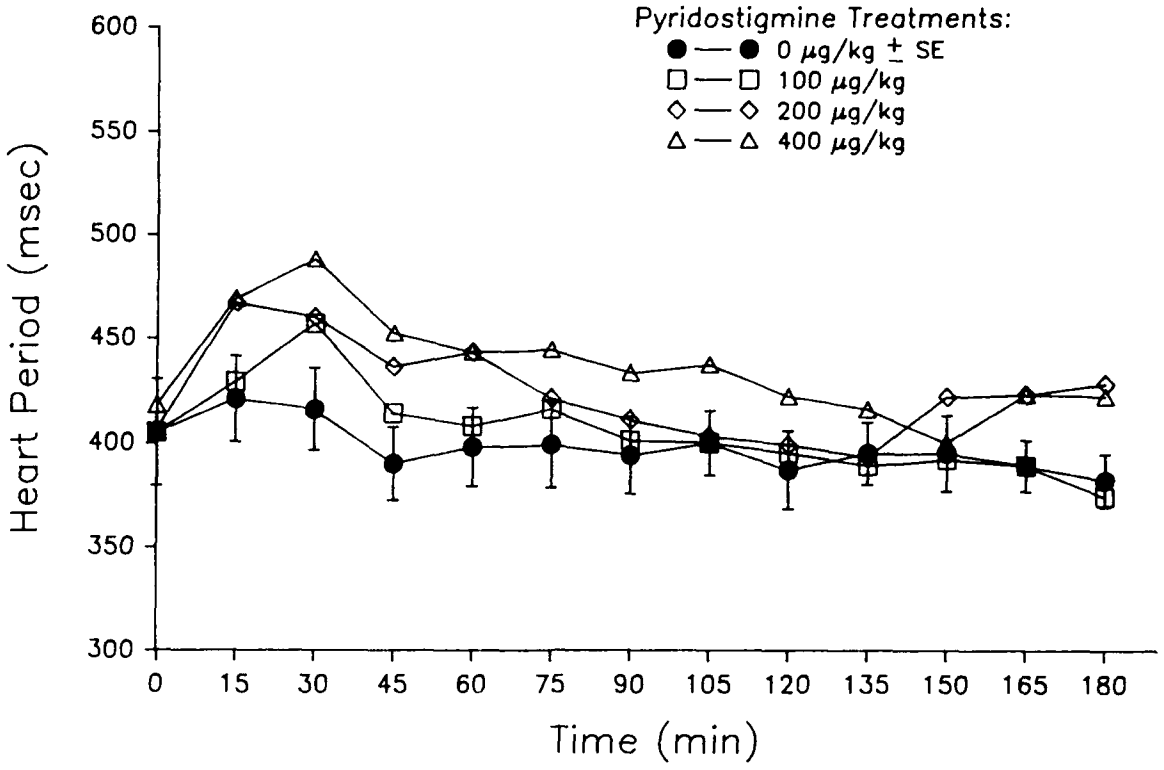

Figure 6. Mean heart period responses vs. time for 4 pyridostigmine bromide treatment conditions (n = 12).

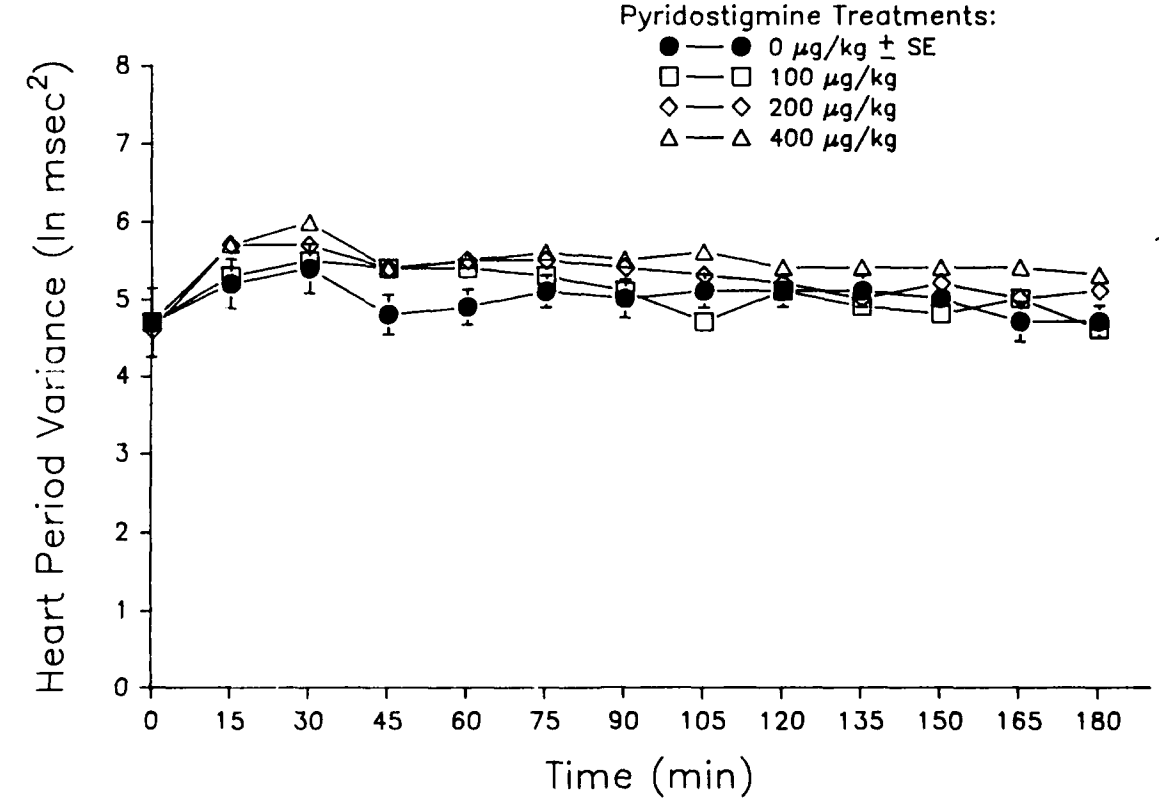

Figure 7. Mean heart period variance responses vs. time for 4 pyridostigmine bromide treatment conditions (n = 12).

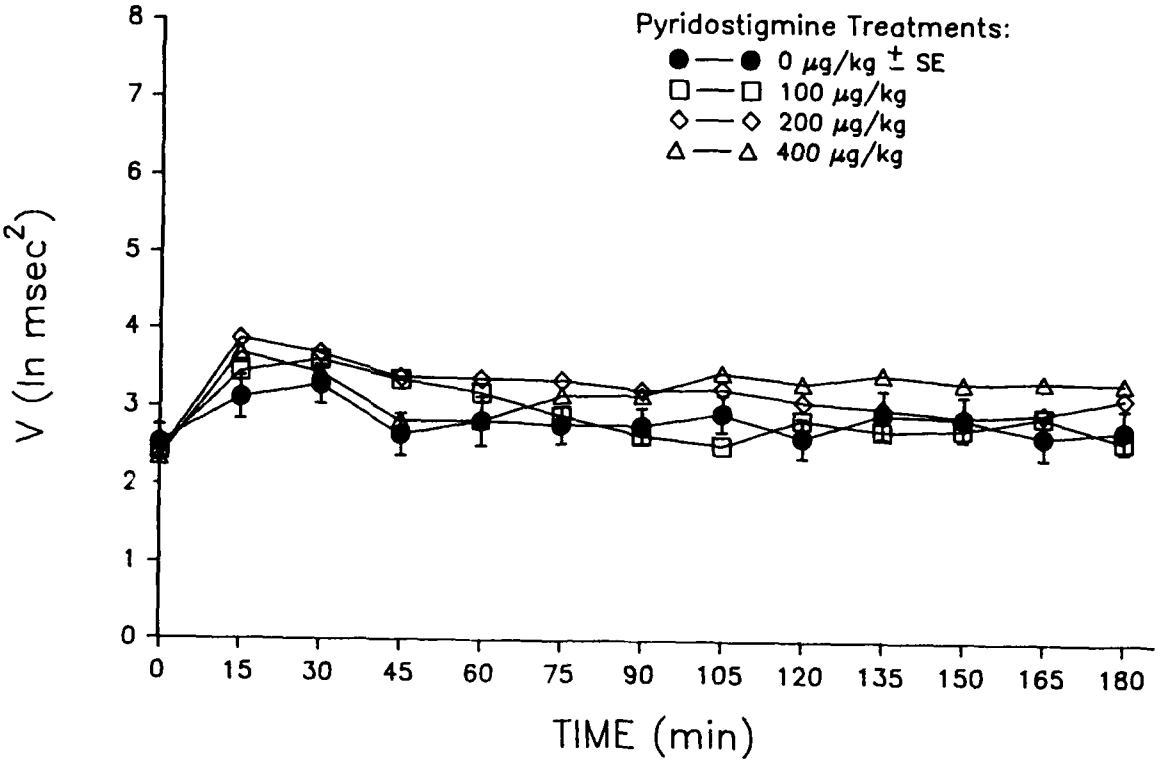

Figure 8. Mean estimate of vagal tone responses vs. time for 4 pyridostigmine bromide treatment conditions (n = 12).

There was a significant dose effect for V between the control and high (400 µg) dose at 165 min. There was also a significant difference at 135 min between the high (400 µg) and low (100 µg) doses. However, we should note here that the rather random significant differences, as indicated by the Tukey's contrasts for V, reflected the lack of a dose effect in the ANOVA. The significant dose*time interaction for V was likely due to the tendency of an increase in V during the first hour for all doses and placebo and the apparent increase during the last 90 min for the high (400 µg) dose. However, these effects are small in magnitude when compared to the changes observed for atropine sulfate (Experiment 1) and physostigmine (Experiment 4).

P-Q Intervals

There were no significant dose or dose*time effects for the P-Q interval in response to pyridostigmine bromide (Appendix H).

Cardiology

Visual examination of electrocardiogram traces showed no readily apparent anomalies. One animal had exceptionally high P-waves which is consistent with right atrial enlargement. A different animal had inverted P-waves on ECG traces throughout the experimental sessions. No other significant aberrations or arrhythmias were evident.

Cholinesterase

Mean plasma ChE activity was significantly depressed from controls in a dose dependent fashion (Fig. 9, Appendixes I and J). At 30 min post dose, mean plasma ChE inhibitions of 18%, 40%, and 57% resulted from administration of the 100-, 200-, and 400-µg doses, respectively.

At 180 min post dose, plasma cholinesterase activity had recovered slightly with inhibitions of 13%, 37%, and 49%, respectively. Although slight recovery of cholinesterase activity did occur at 180 min, enzyme activity remained significantly depressed from baseline/control levels.

Mean erythrocyte ChE was also significantly depressed from controls in a dose-responsive manner (Fig. 10). At 30 min post dose, mean erythrocyte ChE inhibitions of 36%, 59%, and 69% resulted from administration of 100-, 200-, and 400-µg doses, respectively.

Significant recovery of erythrocyte ChE activity occurred at 180 min post dose for all dose levels, yet activity was still significantly depressed from control levels. Mean ChE inhibitions at 180 min post dose were 3%, 18%, and 35%.

Experiment III (Pyridostigmine Bromide plus Atropine Sulfate)

Vagal Tone Monitoring

All four variables tested (HR, HP, HPV, and V) showed a significant dose effect and a significant dose*time interaction (Figs. 11-13, HR not shown; Tables 16-20; Appendixes K and L). Although there was also a group effect for all four variables, the group*dose and group*time interactions were not significant for any of the variables.

All animals exhibited a decrease in HR and a corresponding increase in HP, HPV, and V at both 15 min and 30 min after receiving 200 µg of pyridostigmine (Tables 17-20). These results concur with the response to the mid dose in Experiment II. All variables exhibited a peak response to the 44- and 140-µg/kg atropine sulfate doses between 60 min and 75 min (30 min and 45 min after atropine; Figs 11-13). This time also corresponds to the time of the peak response in Experiment I.

There was no significant difference between the 14-µg/kg dose and the 0-µg/kg dose at any time for any of the 4 VTM parameters measured

(Tables 17-20). Heart rate was significantly less for the 140-µg/kg and 44-µg/kg doses than for the 0-µg/kg treatment between 60 min and 135 min, but they were not significantly different from each other. Heart period followed the same trend as HR with both the 44- and 140-µg/kg doses significantly decreased compared to the placebo dose but not different from each other.

Heart period variance exhibited a dose-response relationship to atropine following the pyridostigmine pretreatment (Table 19; Fig. 12). The 14-µg/kg dose of atropine did not produce a response significantly different from that of the placebo (200-µg/kg pyridostigmine, no atropine), but all other comparisons using the Tukey's Studentized Range Test between 60 min and 180 min indicated a significantly different response to each dose of atropine.

There was a significant dose effect for V, and this estimate of RSA was decreased to near zero after the 140-µg/kg dose and was not distinguishable from the response to the 44-µg/kg dose (Fig. 13, Table 20). Both the 44- and 140-µg/kg doses decreased the level of V between 60 min and 180 min.

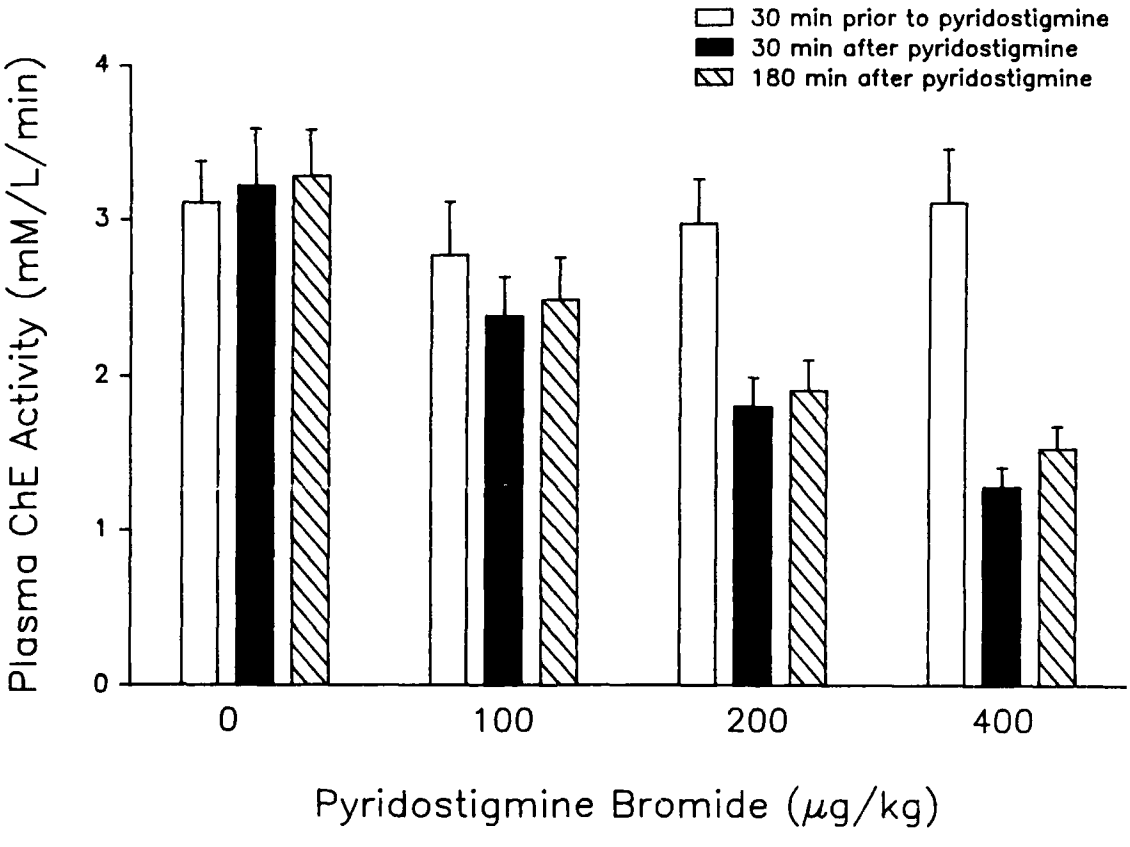

Figure 9. Mean plasma cholinesterase for 4 pyridostigmine bromide treatment conditions (n = 12) (Experiment II).

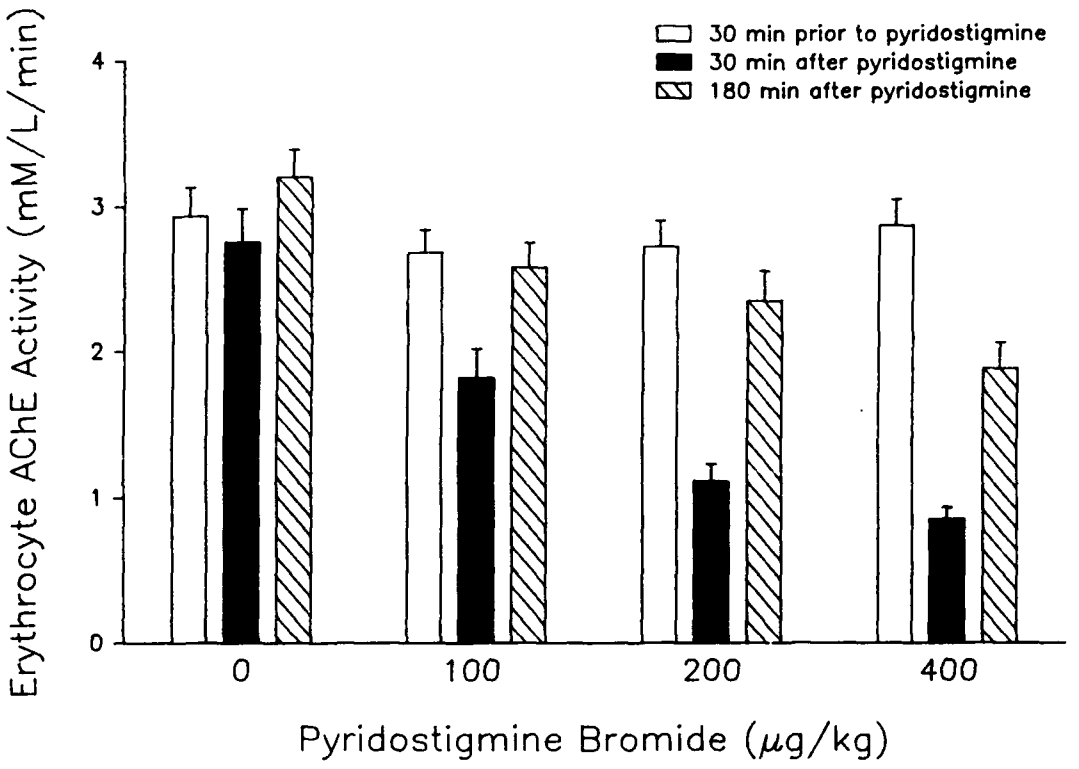

Figure 10. Mean erythrocyte cholinesterase activity for 4 pyridostigmine bromide treatment conditions (n = 12) (Experiment II).

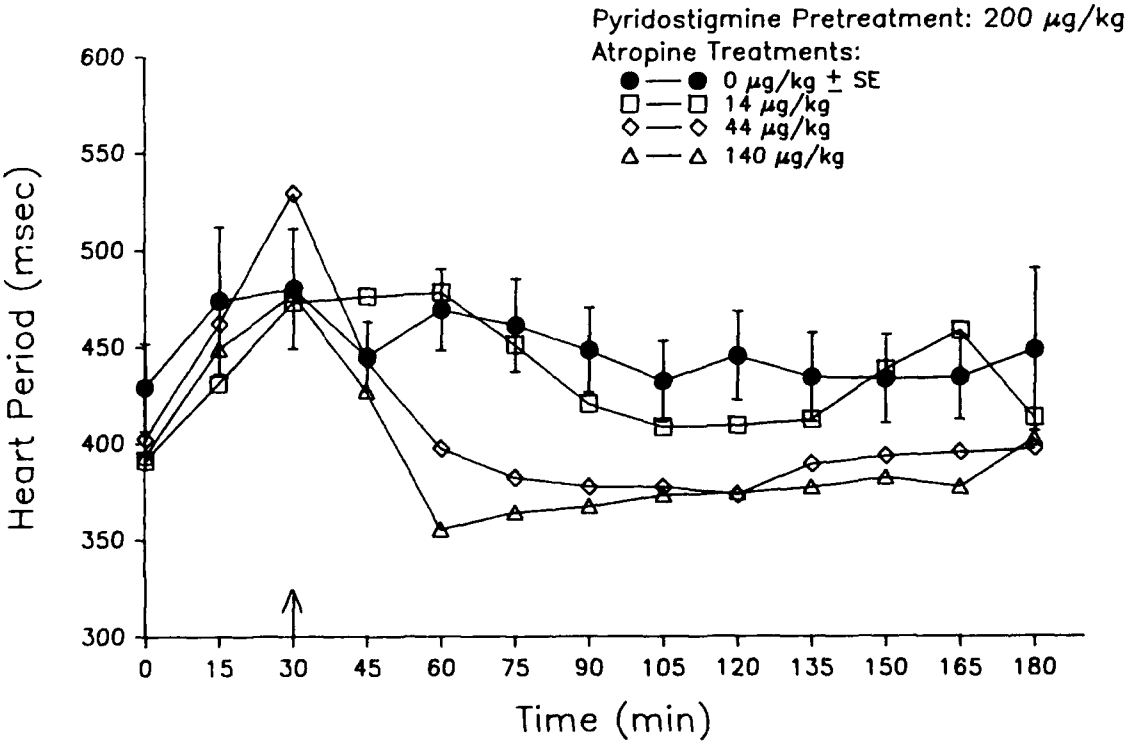

Figure 11. Mean heart period responses vs. time for 4 atropine sulfate treatment conditions following pyridostigmine bromide pretreatment (n = 12).

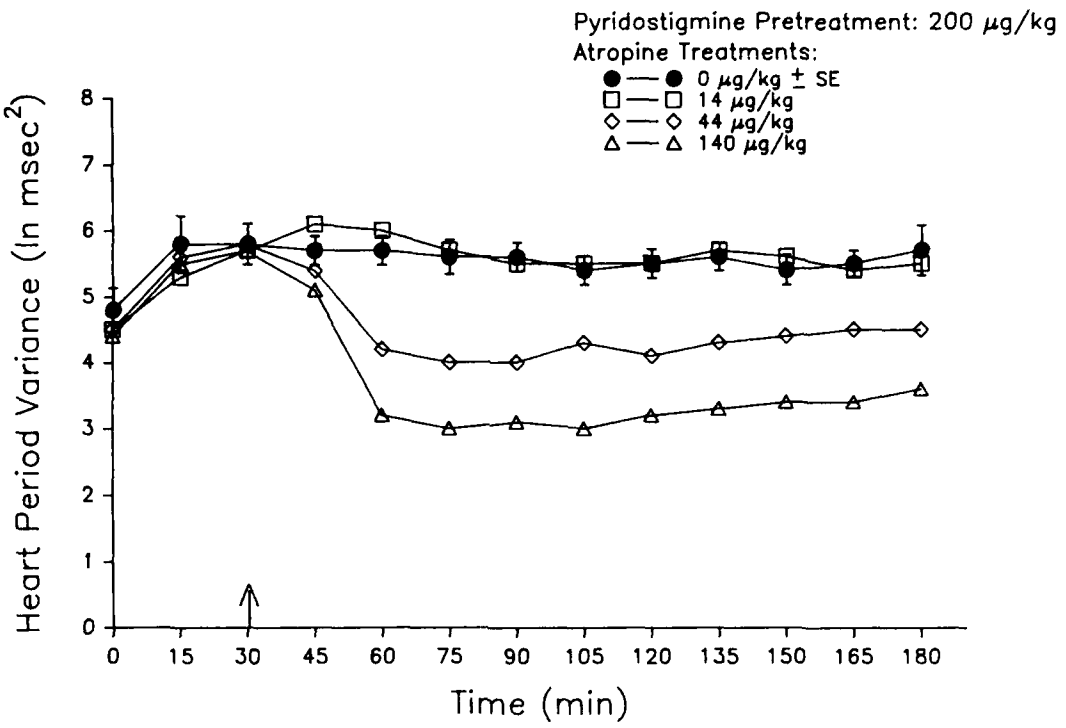

Figure 12. Mean heart period variance responses vs. time for 4 atropine sulfate treatment conditions following pyridostigmine bromide pretreatment (n = 12).

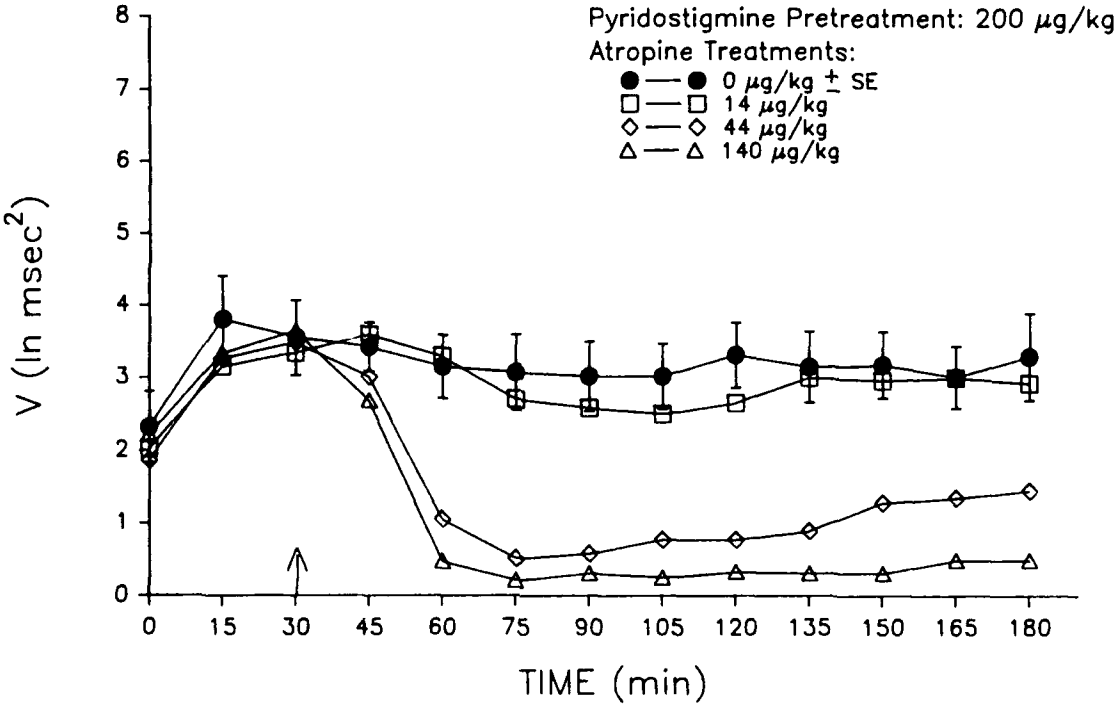

Figure 13. Mean estimate of vagal tone responses vs. time for 4 atropine sulfate treatment conditions following pyridostigmine bromide pretreatment (n = 12).

TABLE 16. F-RATIOS AND PROBABILITIES FOR MAIN AND INTERACTIVE EFFECTS AFTER PYRIDOSTIGMINE/ATROPINE COMBINATION IN THE RHESUS MONKEY

Dependent variable	F-ratios		
	Dose*time	Dose	Time
HR	4.56 P < .0001	9.35 P < .0003	17.00 P < .0001
HP	2.89 P < .0001	5.84 P < .004	10.87 P < .0001
HPV	10.55 P < .0001	45.34 P < .0001	20.83 P < .0001
V	8.75 P < .0001	24.08 P < .0001	43.23 P < .0001
Erythrocyte ChE	0.70 P < .650	0.96 P < .426	239.73 P < .0001
Plasma ChE	0.70 P < .647	16.36 P < .0001	56.69 P < .0001

TABLE 17. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR HEART RATE

Trt. contrast (µg/kg)	Time after pyridostigmine bromide injection					
	15	30	45	60	75	90
0 to 14	NS	NS	NS	NS	NS	NS
0 to 44	NS	NS	NS	*	*	*
0 to 140	NS	NS	NS	*	*	*
14 to 44	NS	NS	NS	*	*	*
14 to 140	NS	NS	NS	*	*	*
44 to 140	NS	NS	NS	NS	NS	NS

Trt. contrast (µg/kg)	Time after pyridostigmine bromide injection					
	105	120	135	150	165	180
0 to 14	NS	*	NS	NS	NS	NS
0 to 44	*	*	*	NS	NS	NS
0 to 140	*	*	*	NS	*	NS
14 to 44	NS	*	NS	NS	NS	NS
14 to 140	*	*	*	NS	*	NS
44 to 140	NS	NS	NS	NS	NS	NS

*Contrast is significant, $p < 0.05$.

TABLE 18. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR HEART PERIOD

Trt. contrast (μg/kg)	Time after pyridostigmine bromide injection					
	15	30	45	60	75	90
0 to 14	NS	NS	NS	NS	NS	NS
0 to 44	NS	NS	NS	*	*	*
0 to 140	NS	NS	NS	*	*	*
14 to 44	NS	NS	NS	*	*	*
14 to 140	NS	NS	NS	*	*	*
44 to 140	NS	NS	NS	NS	NS	NS

Trt. contrast (μg/kg)	Time after pyridostigmine bromide injection					
	105	120	135	150	165	180
0 to 14	NS	*	NS	NS	NS	NS
0 to 44	*	*	*	NS	NS	NS
0 to 140	*	*	*	NS	NS	NS
14 to 44	NS	*	NS	NS	NS	NS
14 to 140	*	NS	*	NS	NS	NS
44 to 140	NS	NS	NS	NS	NS	NS

*Contrast is significant, $p < 0.05$.

TABLE 19. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR HEART PERIOD VARIANCE

Trt. contrast (μg/kg)	Time after pyridostigmine bromide injection					
	15	30	45	60	75	90
0 to 14	NS	NS	NS	NS	NS	NS
0 to 44	NS	NS	NS	*	*	*
0 to 140	NS	NS	NS	*	*	*
14 to 44	NS	NS	NS	*	*	*
14 to 140	NS	NS	*	*	*	*
44 to 140	NS	NS	NS	*	*	*

Trt. contrast (μg/kg)	Time after pyridostigmine bromide injection					
	105	120	135	150	165	180
0 to 14	NS	NS	NS	NS	NS	NS
0 to 44	*	*	*	*	*	*
0 to 140	*	*	*	*	*	*
14 to 44	*	*	*	*	*	*
14 to 140	*	*	*	*	*	*
44 to 140	*	*	*	*	*	*

*Contrast is significant, $p < 0.05$.

TABLE 20. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR VAGAL TONE

Trt. contrast (μg/kg)	Time after pyridostigmine bromide injection					
	15	30	45	60	75	90
0 to 14	NS	NS	NS	NS	NS	NS
0 to 44	NS	NS	NS	*	*	*
0 to 140	NS	NS	NS	*	*	*
14 to 44	NS	NS	NS	*	*	*
14 to 140	NS	NS	NS	*	*	*
44 to 140	NS	NS	NS	NS	NS	NS

Trt. contrast (μg/kg)	Time after pyridostigmine bromide injection					
	105	120	135	150	165	180
0 to 14	NS	NS	NS	NS	NS	NS
0 to 44	*	*	*	*	*	*
0 to 140	*	*	*	*	*	*
14 to 44	*	*	*	*	*	*
14 to 140	*	*	*	*	*	*
44 to 140	NS	NS	NS	NS	NS	NS

*Contrast is significant, $p < 0.05$.

P-Q Intervals

During the 15 min following administration of 200 μg of pyridostigmine bromide, there was an overall (but not significant) trend towards an increased P-Q interval (Table 21; Appendix M). After the atropine administration, only the 44-μg/kg dose significantly decreased the mean conduction time at the AV node. The P-Q intervals of the 44-μg/kg dose were significantly less than the placebo levels from 10 min until 60 min post atropine administration. The overall dose*time interaction was not significant.

Cardiology

The monkey which exhibited premature ventricular beats during Experiment I no longer showed this phenomenon during the 4 weeks in which it received the pyridostigmine/atropine combination. However, another monkey did exhibit several premature ventricular beats during the 4 weeks of Experiment III. The frequency of this phenomenon did not seem to change after either pyridostigmine or atropine administration. Another monkey exhibited a very small R-wave and a large S-wave. Several of the monkeys showed a transient inversion of the P-wave, although this also occurred before the administration of any drugs. Therefore, no drug-related cardiac complications were observed.

Cholinesterase

All animals received 200 μg of pyridostigmine bromide per kilogram body weight for all 4 weeks of this experiment. Significant individual variability was expected both in baseline ChE activity and in the response to pyridostigmine and produced a large F-statistic which was accounted for in the overall statistical model by partitioning out the appropriate error term. There was a significant decrease from baseline ChE activity at 30 min post pyridostigmine dosing for both plasma and red blood cells (RBC) (32% inhibition, 54% inhibition respectively) (Figs. 14 and 15). There was a significant recovery toward baseline erythrocyte ChE level (15% inhibited) 180 min post dosing, but no recovery in plasma ChE activity (33% inhibited).

There was no significant atropine-related dose effect on erythrocyte ChE (Appendixes N and O). The baseline plasma ChE activity for the 44-μg/kg dose was significantly higher, causing the dose response for plasma ChE. A significant dose effect for plasma ChE was observed but was not due to atropine since this was significant only during the baseline period for the 44-μg/kg dose and disappeared after atropine administration. There was no atropine-related dose*time interaction for either plasma or erythrocyte ChE. Although there was a significant week effect for both erythrocyte and plasma ChE activity, this was due to Week 1 having a consistently lower ChE activity than the other experimental weeks. The lower Week 1 activity may have been due to a change in ambient temperature or the reagents used during that week.

Probit Analysis

The ED_{50} for HPV and V were determined from the VTM data. A 30% decrease in HPV and V in the presence of pyridostigmine was used for comparison to Experiment I. The number of animals that responded at each dose was used to estimate the ED_{50}. The ED_{50} for HPV was estimated to be 112.7 μg/kg (range 69.8-338.3; χ^2 [1, N = 2] = 0.1782, $p > 0.6730$) and for V was estimated to be 18.3 μg/kg (range 4.6-31.9; χ^2 [1, N = 2] = 2.3927, $p > 0.1219$). The estimate of RSA (V) was determined to be more sensitive than HPV to the anticholinergic effects of atropine sulfate even in the presence of pyridostigmine bromide. In comparison, the ED_{50} calculated for atropine in Experiment I was 29 μg/kg for HPV and 9 μg/kg for V.

Experiment IV (Physostigmine Salicylate)

Vagal Tone Monitoring

All four parameters (HR, HP, HPV, and V) were measured after administration of physostigmine salicylate. Figures 16-18 illustrate the effects of physostigmine, and Table 22 contains the summary of the full ANOVAs (Appendixes P and Q). No significant dose effect was observed for HR, and HP (Fig. 16 [HR not shown]; Table 22). The HPV and V had significant dose*time interactions after administration of physostigmine salicylate (Figs. 17 and 18; Table 22). There was also a significant time effect for both HPV and V, but not for HP and HR (Table 22).

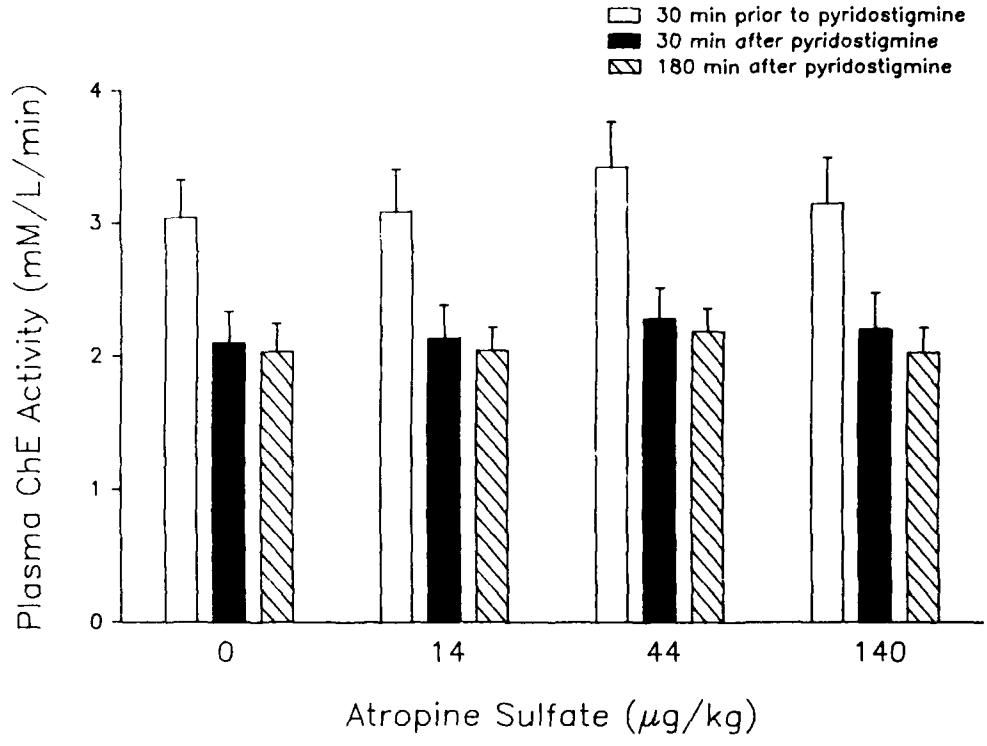

Figure 14. Mean plasma cholinesterase activity for 4 atropine sulfate treatment conditions following pyridostigmine pretreatment (n = 12) (Experiment III).

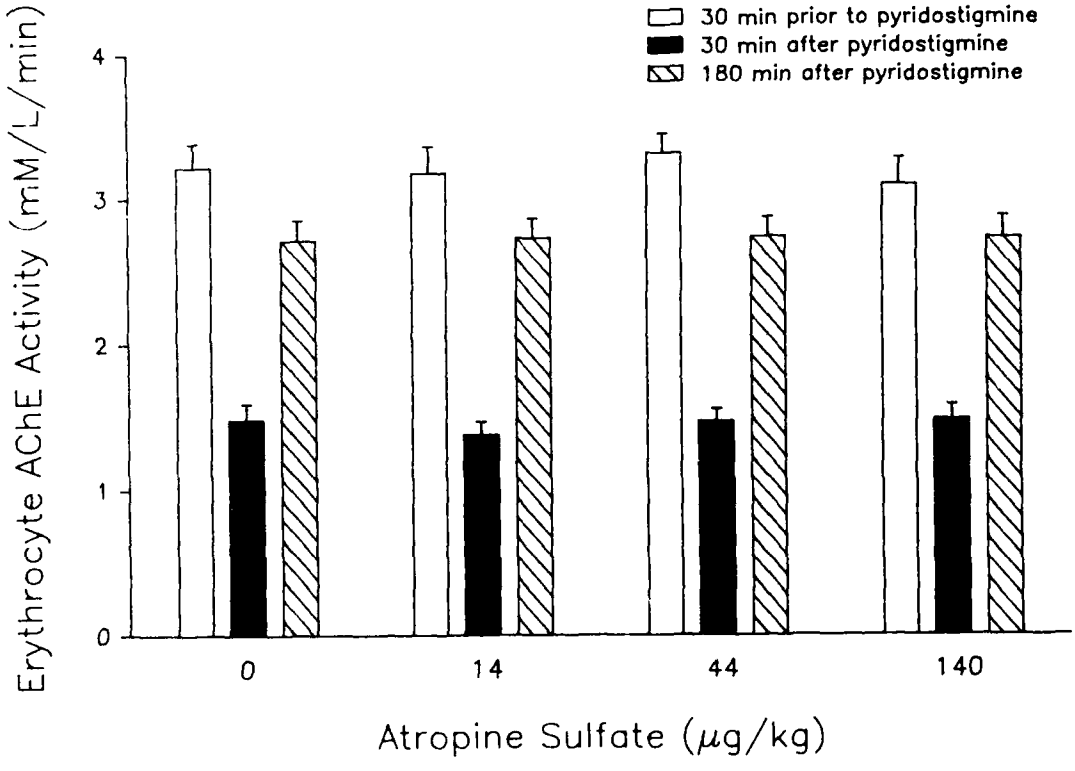

Figure 15. Mean erythrocyte cholinesterase activity for 4 atropine sulfate treatment conditions following pyridostigmine bromide pretreatment (n = 12) (Experiment III).

TABLE 21. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR P-Q INTERVALS

Trt. contrast (µg/kg)	Time after pyridostigmine bromide injection					
	15	30	45	60	75	90
0 to 14	NS	NS	*	NS	NS	NS
0 to 44	NS	*	*	*	*	*
0 to 140	NS	NS	NS	NS	NS	*
14 to 44	NS	*	*	NS	NS	NS
14 to 140	NS	NS	*	NS	NS	NS
44 to 140	NS	NS	NS	NS	NS	NS

Trt. contrast (µg/kg)	Time after pyridostigmine bromide injection					
	105	120	135	150	165	180
0 to 14	NS	NS	NS	NS	NS	NS
0 to 44	NS	NS	NS	*	NS	NS
0 to 140	NS	NS	NS	NS	NS	*
14 to 44	NS	NS	NS	NS	NS	*
14 to 140	NS	NS	NS	NS	NS	*
44 to 140	NS	NS	NS	NS	NS	NS

*Contrast is significant, $p < 0.05$.

The Tukey's contrasts for treatments are listed in Tables 23-26 for HR, HP, HPV, and V. There were no significant dose effects or dose*time interactions for HR and HP (Tables 23 and 24). Although HPV and V did not exhibit significant dose*time effects after administration of physostigmine salicylate, the responses (Figs. 17 and 18) indicate that the HPV and V increased for the lowest dose (25 µg/kg) and decreased for the highest dose (100 µg/kg) during the first hour, followed by an increase in HPV and V for all physostigmine treatments during the last 90 min. The Tukey's contrasts indicate that these effects are most apparent for the 25- vs. the 100-µg doses during the first hour for HPV and V, and the 50- and 100-µg doses vs. the control during the last 30 min for HPV (Tables 25 and 26). The magnitude of the physostigmine effects is apparently greater for V than for HPV (compare Figs. 17 and 18).

P-Q Intervals

There were no significant dose effects, interactions or time effects following administration of physostigmine salicylate (Appendix R).

Cardiology

Visual examination of ECG traces revealed no notable aberrations or arrhythmias attributable to administration of physostigmine. The animal displaying an enlarged P-Q wave in Experiment II did not exhibit the anomaly during this phase of the study.

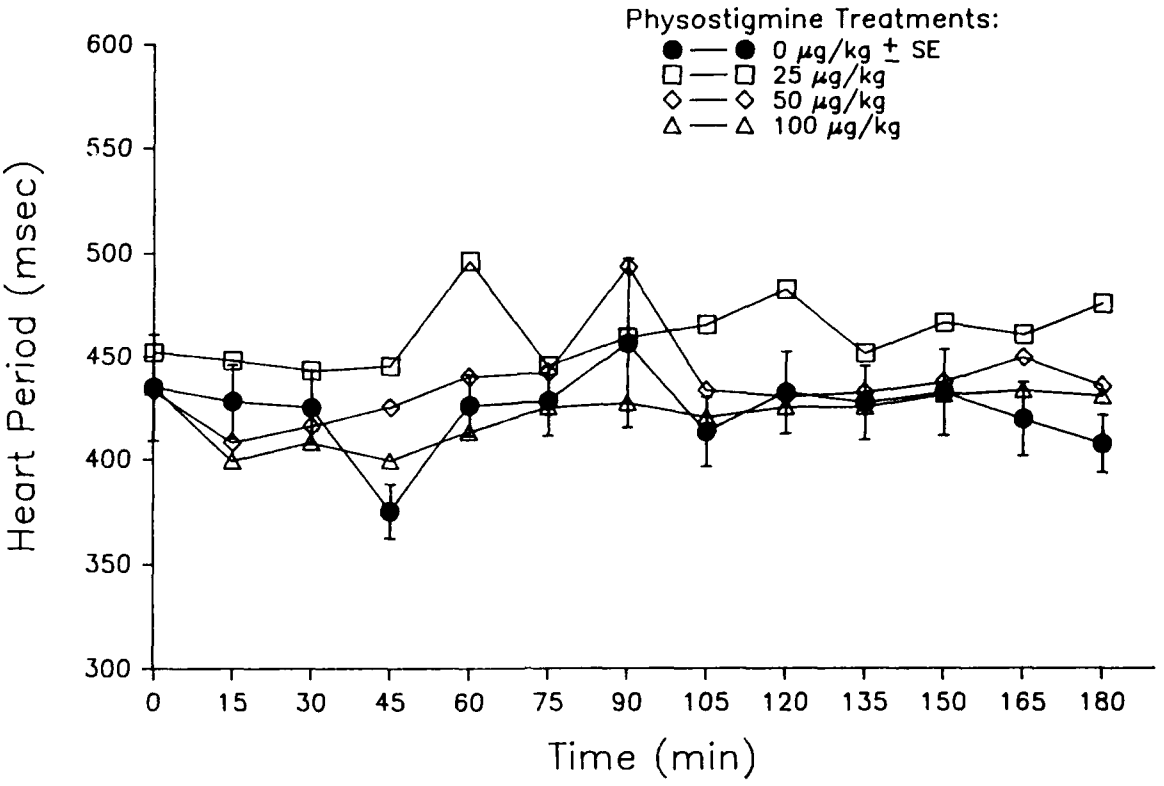

Figure 16. Mean heart period responses vs. time for 4 physostigmine treatment conditions (n = 12).

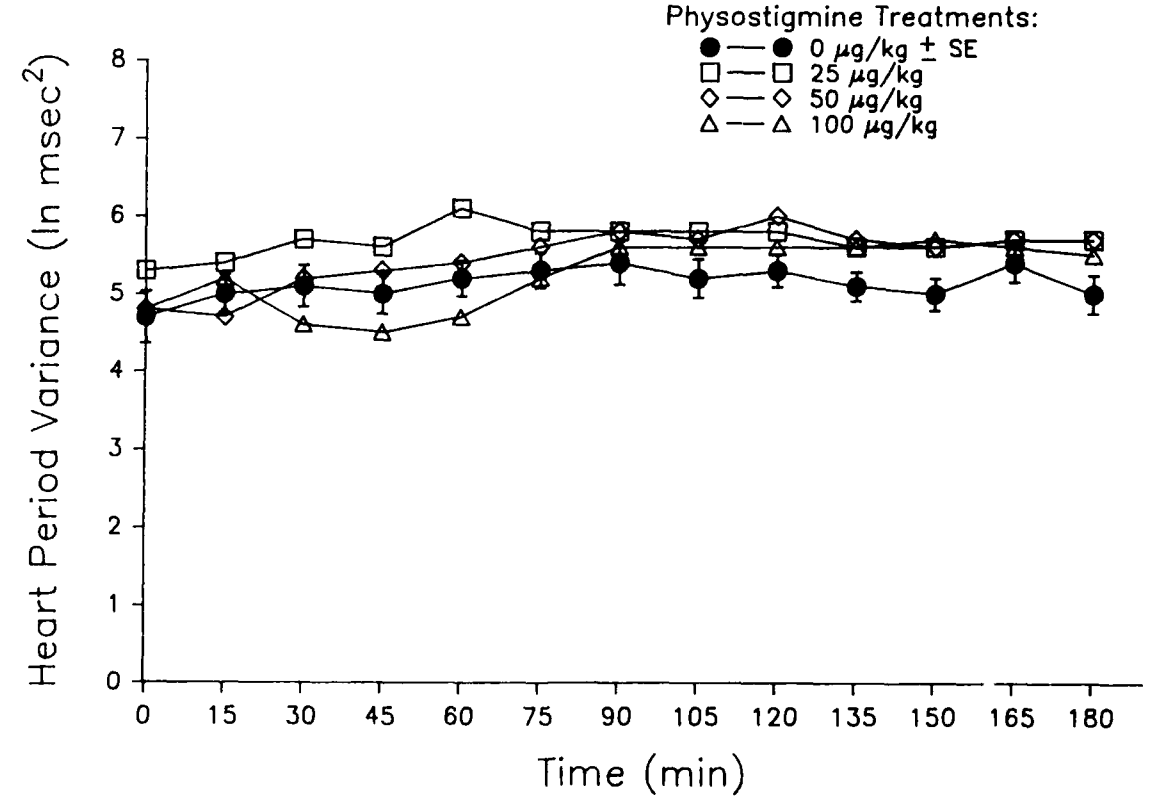

Figure 17. Mean heart period variance responses vs. time for 4 physostigmine treatment conditions (n = 12).

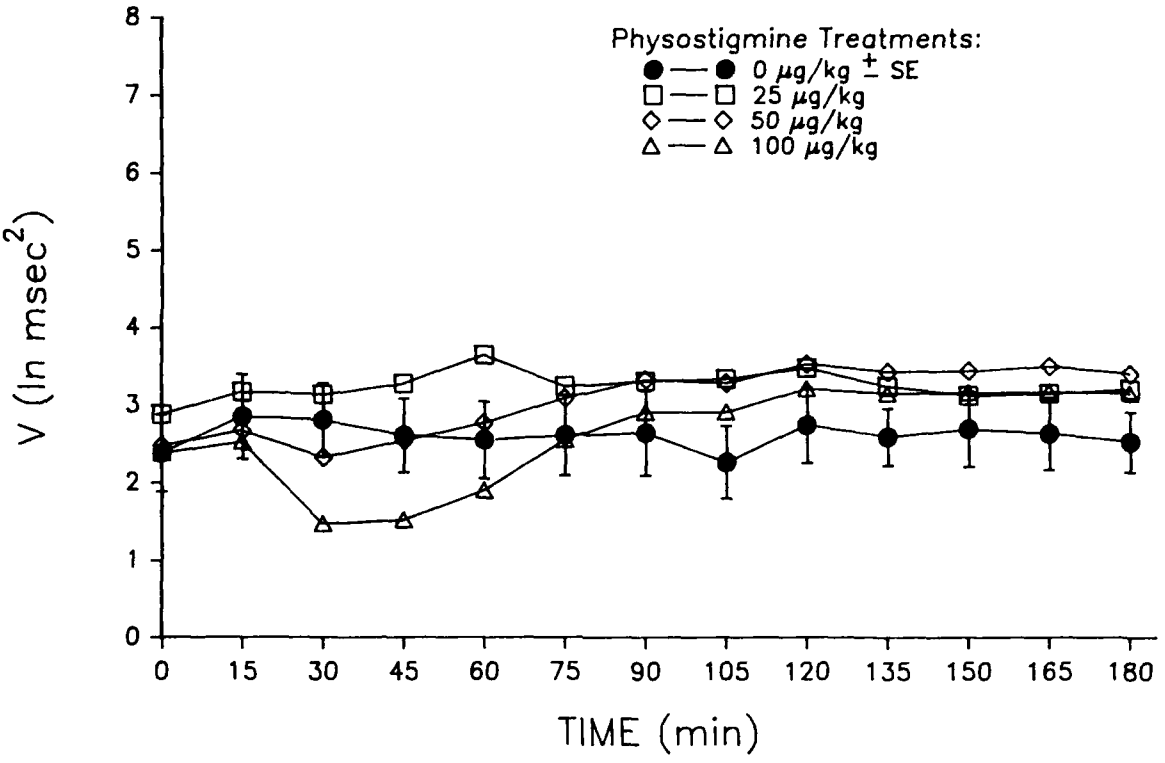

Figure 18. Mean estimate of vagal tone (V) responses vs. time for 4 physostigmine salicylate treatment conditions (n = 12).

Cholinesterase

Mean plasma ChE activity was significantly depressed from control values at all dose levels (Fig. 19; Appendixes S and T). Enzyme inhibition was not significantly different between the 50- and 100-µg doses. In addition, ChE inhibition was not significantly different between the 25- and 50-µg doses. There was a significant difference between ChE inhibition for the 25- and 100-µg doses.

At 30 min post dose, mean plasma ChE inhibitions of 53%, 63%, and 74% resulted after administration of 25-, 50-, and 100-µg doses, respectively. At 180 min post dose, mean plasma ChE inhibition had been reduced to 25%, 39%, and 57%, respectively. Although this recovery from the 30 min post dose levels was statistically significant, ChE activity still remained significantly less than control levels.

Mean erythrocyte ChE activity was significantly depressed from control levels for all dose levels (Fig. 20; Appendix R). At 30 min post dose, mean erythrocyte ChE inhibitions of 26%, 34%, and 50% resulted from administration of 25-, 50-, and 100-µg doses, respectively. Additionally, ChE inhibition was significantly different only between the 25- and 100-µg doses, but no significant differences existed between the 25- and 50-µg doses or the 50- and 100-µg doses.

TABLE 22. F-RATIOS AND PROBABILITIES FOR MAIN AND INTERACTIVE EFFECTS AFTER PHYSOSTIGMINE IN THE RHESUS MONKEY

Dependent variable	F-ratios		
	Dose*time	Dose	Time
HR	1.25 P < .174	1.38 P < .274	1.76 P < .074
HP	1.02 P < .445	1.61 P < .213	1.74 P < .077
HPV	2.74 P < .0001	1.69 P < .195	2.74 P < .004
V	4.00 P < .0001	1.58 P < .220	2.59 P < .007
Erythrocyte ChE	14.48 P < .0001	9.24 P < .0003	80.16 P < .0001
Plasma ChE	29.03 P < .0001	46.99 P < .0001	53.73 P < .0001

TABLE 23. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR HEART RATE

Trt. contrast (µg/kg)	Time after physostigmine salicylate injection					
	15	30	45	60	75	90
0 to 25	NS	NS	*	NS	NS	NS
0 to 50	*	NS	*	NS	NS	NS
0 to 100	*	NS	NS	*	NS	NS
25 to 50	NS	NS	NS	NS	NS	NS
25 to 100	NS	NS	NS	NS	NS	NS
50 to 100	NS	NS	NS	NS	NS	NS

Trt. Contrast (µg/kg)	Time after physostigmine salicylate injection					
	105	120	135	150	165	180
0 to 25	NS	NS	NS	NS	NS	NS
0 to 50	NS	NS	NS	NS	NS	NS
0 to 100	NS	NS	NS	NS	NS	NS
25 to 50	NS	NS	NS	NS	NS	NS
25 to 100	NS	NS	NS	NS	NS	NS
50 to 100	NS	NS	NS	NS	NS	NS

*Contrast is significant, $p < 0.05$.

TABLE 24. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR HEART PERIOD

Trt. contrast (µg/kg)	Time after physostigmine salicylate injection					
	15	30	45	60	75	90
0 to 25	NS	NS	*	NS	NS	NS
0 to 50	NS	NS	NS	NS	NS	NS
0 to 100	NS	NS	NS	NS	NS	NS
25 to 50	NS	NS	NS	NS	NS	NS
25 to 100	*	NS	NS	*	NS	NS
50 to 100	NS	NS	NS	NS	NS	NS

Trt. contrast (µg/kg)	Time after physostigmine salicylate injection					
	105	120	135	150	165	180
0 to 25	NS	NS	NS	NS	NS	NS
0 to 50	NS	NS	NS	NS	NS	NS
0 to 100	NS	NS	NS	NS	NS	NS
25 to 50	NS	NS	NS	NS	NS	NS
25 to 100	NS	NS	NS	NS	NS	NS
50 to 100	NS	NS	NS	NS	NS	NS

*Contrast is significant, $p < 0.05$.

TABLE 25. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR HEART PERIOD VARIANCE

Trt. contrast (µg/kg)	Time after physostigmine salicylate injection					
	15	30	45	60	75	90
0 to 25	NS	NS	NS	NS	NS	NS
0 to 50	NS	NS	NS	NS	NS	NS
0 to 100	NS	NS	NS	NS	NS	NS
25 to 50	NS	NS	NS	NS	NS	NS
25 to 100	NS	NS	*	*	NS	NS
50 to 100	NS	NS	NS	NS	NS	NS

Trt. contrast (µg/kg)	Time after physostigmine salicylate injection					
	105	120	135	150	165	180
0 to 25	NS	NS	NS	NS	NS	NS
0 to 50	NS	NS	NS	*	NS	*
0 to 100	NS	NS	NS	*	NS	*
25 to 50	NS	NS	NS	NS	NS	NS
25 to 100	NS	NS	NS	NS	NS	NS
50 to 100	NS	NS	NS	NS	NS	NS

*Contrast is significant, $p < 0.05$.

TABLE 26. SUMMARY OF THE TUKEY'S STUDENTIZED RANGE CONTRASTS FOR VAGAL TONE

Trt. contrast (µg/kg)	Time after physostigmine salicylate injection					
	15	30	45	60	75	90
0 to 25	NS	NS	NS	NS	NS	NS
0 to 50	NS	NS	NS	NS	NS	NS
0 to 100	NS	NS	NS	NS	NS	NS
25 to 50	NS	NS	NS	NS	NS	NS
25 to 100	NS	*	*	*	NS	NS
50 to 100	NS	NS	NS	NS	NS	NS

Trt. contrast (µg/kg)	Time after physostigmine salicylate injection					
	105	120	135	150	165	180
0 to 25	NS	NS	NS	NS	NS	NS
0 to 50	NS	NS	NS	NS	NS	NS
0 to 100	NS	NS	NS	NS	NS	NS
25 to 50	NS	NS	NS	NS	NS	NS
25 to 100	NS	NS	NS	NS	NS	NS
50 to 100	NS	NS	NS	NS	NS	NS

*Contrast is significant, $p < 0.05$.

Significant recovery of enzyme activity was evident at 180 min postdose. Mean erythrocyte inhibitions resulting from administration of low, mid, and high doses were 6.2%, 8%, and 26%, respectively. Although some recovery did occur, ChE activity was still significantly depressed from control levels.

A significant week effect was observed during this phase of the experiment for both plasma and erythrocyte ChE activity. This effect appears to be due to the difference between Week 4 of the experimental session and the preceding 3 weeks.

DISCUSSION

The four experiments described here demonstrate the usefulness of the VTM in monitoring anticholinergic and anticholinesterase treatments in rhesus monkeys. Previous work by Dellinger et al. (13) clearly depicted the muscarinic blockade of vagal tone by atropine sulfate in humans and the attenuated response to atropine following anticholinesterase OP exposures in the dog (3,37). The present studies are in agreement with both the human atropine response and the dog attenuated atropine response.

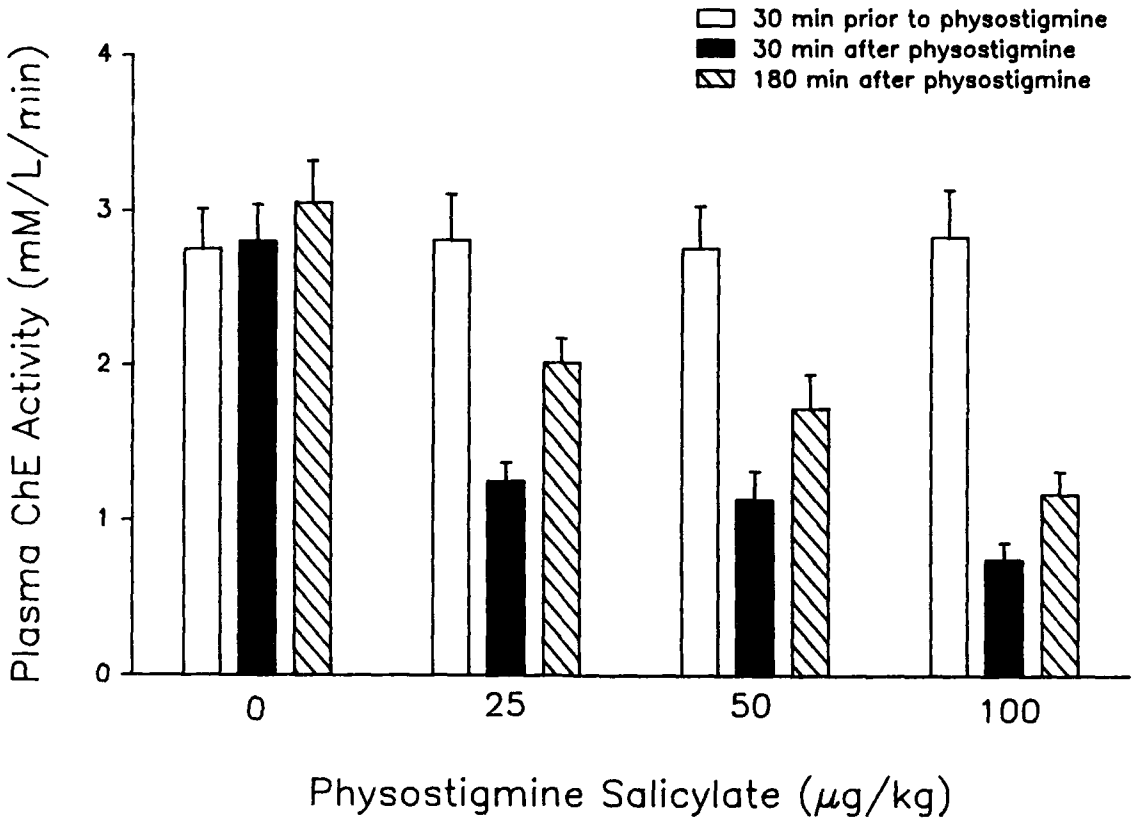

Figure 19. Mean plasma cholinesterase activity for 4 physostigmine salicylate treatment conditions (n = 12) (Experiment IV).

Experiment I demonstrated that the rhesus monkey is an adequate model of the human using the VTM. Whereas HP returned to near basal levels after 75 to 90 min, the RSA amplitude remained depressed for nearly 3 h and suggests that the administration of atropine sulfate in the rhesus monkey produces both peripheral and CNS effects. The estimate of RSA amplitude (V) is a more sensitive indicator of the CNS effects of atropine sulfate than HPV, HP, or HR. The sensitivity of V is in agreement with the findings of Dellinger et al. (13) in humans. The VTM response to atropine is most clearly seen at the 14-μg dose in which V did not fall to zero; mean depression in V is greater than the decrease in HPV.

Absolute quantification of the degree of influence of sympathetic tone on RSA is complicated by the presence of nonneuronal and hormonal factors. However, the slow wave frequency, which is believed to represent the sympathetic influence on the heart period spectrum (Fig. 5), can be filtered out electronically. In these monkeys, the removal of the slow wave (sympathetic) component of HPV to estimate V resulted in approximately a 2.5-log decrease between these 2 parameters (compare Figs. 2 and 3). The extent of the decrease when comparing HPV to V indicates that, in the rhesus monkey, the sympathetic component may contribute the majority of the overall variability in heart period. These findings differ from the human, in which the fast wave (vagal) component is the primary mediator of the variability

in heart period (13). When the slow wave (sympathetic) component of RSA is removed to estimate V in the human, the decrease is only 1.0-log unit, indicating a quantitative but not qualitative difference between rhesus monkeys and humans. Because filtering allows you the removal of the slow wave component, thereby isolating the vagal component, the rhesus monkey can be used as an acceptable model for human exposures to cholinergically active drugs.

The overall lower vagal activity of monkeys (V = 2.0 compared to 7.0 for humans) may explain in part the increased sensitivity of monkeys to the muscarinic blockade by atropine sulfate. Only the lowest dose (14 µg/kg) did not reduce V to near zero, which suggests that in future studies a lower dose might be used rather than the 140-µg/kg high dose in an effort to better define the dose-response relationships after atropine sulfate.

The estimated ED_{50} of 29 µg/kg (4-68 µg/kg) for HPV is similar to that of the human ED_{50} of 23 µg/kg reported by Dellinger et al. (13). The estimated ED_{50} of 9 µg/kg (upper limit of 23 µg/kg) for V is similar but slightly less than the human ED_{50} of 14 µg/kg reported by Dellinger et al. (13).

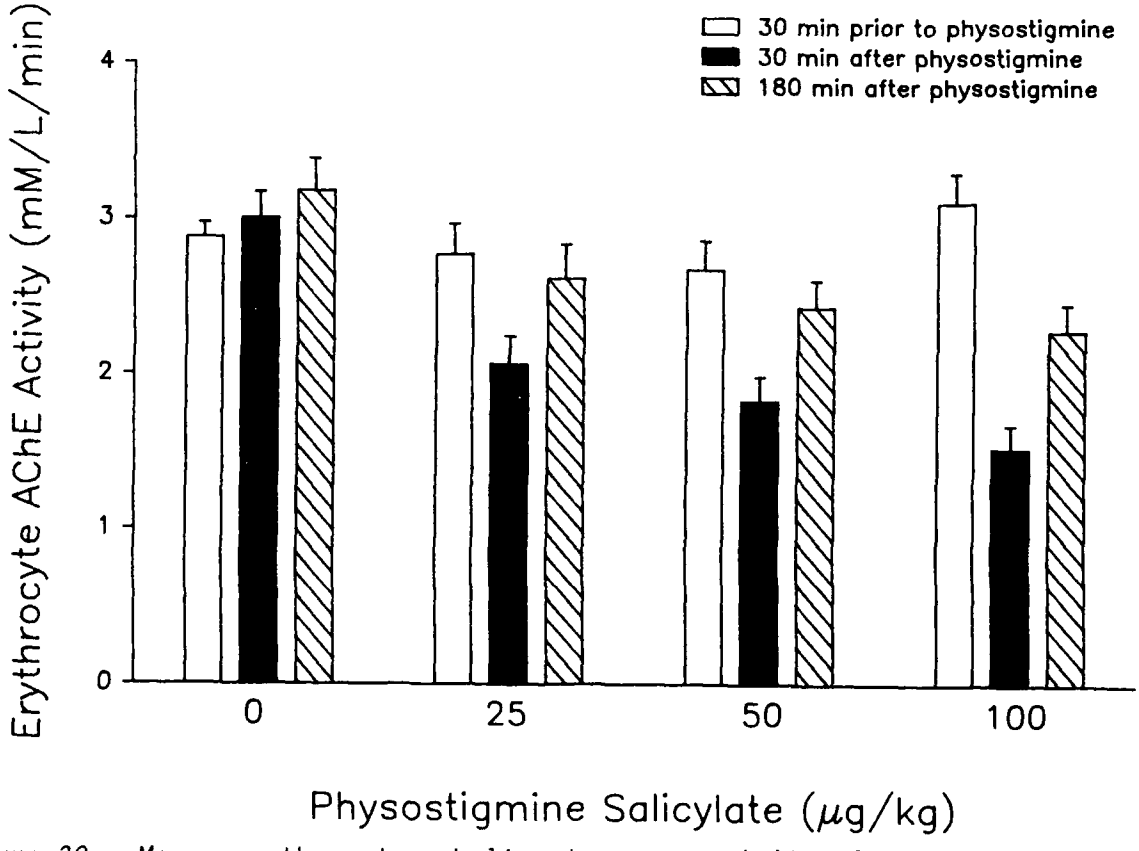

Figure 20. Mean erythrocyte cholinesterase activity for 4 physostigmine salicylate treatment conditions (n = 12) (Experiment IV).

Maximum depression of HPV and V occurred at approximately 45 min after dosing. These findings are consistent with those reported for the human by Dellinger et al. (13) and the dog (3). Therefore, the entry of atropine into the CNS of these three species may be similar. The time point at which V is maximally depressed appears to be independent of the dose, which illustrates the rapid absorption of atropine from the muscle and its subsequent distribution into the brain.

Proakis and Harris (38) found that, in the dog, atropine concentrations in the cerebrospinal fluid (CSF) increased from 10 to 45 to 90 ng/ml at 10 min, 1, and 3 h, respectively. Therefore, if the peak depression of V at 30 to 45 min represents the maximal CNS effect, then a relatively small fraction of the total dose, relative to plasma concentrations, may be sufficient to produce the desired effect. This concentration may be less than expected because of regional differences in the integrity of the blood brain barrier. The area postrema (AP) is known to lack a true blood brain barrier (39). The dorsal vagal nucleus lies just ventrolateral to the AP and might be expected to respond earlier than expected to drugs entering the brain. In addition, the nucleus tractus solitarius (NTS) and nucleus ambiguous (NA), which were proposed to mediate the gating of the integration of respiratory and cardiac information (40), are also located in this region.

An atropine-related decrease in the P-Q interval was observed; however, this effect was weak and reflects the relatively slight increase in heart rate (mean increase = 12 bpm).

In summarizing the results of Experiment I, we concluded that the rhesus monkey provides a useful model for the human in that it responds similarly to atropine sulfate. Heart rate is slightly increased, overall heart rate variability is decreased, the amplitude of RSA is diminished, and the doses required to produce these effects are very similar to those required in the human.

Experiments II, III, and IV included the VTM responses to carbamate anticholinesterase treatments. These experiments allowed us to examine two methods of utilizing the VTM in a field situation. First, if the VTM parameters respond reliably to anticholinesterase exposures, then it may be useful for directly monitoring OP exposures. Second, if the attenuated response to atropine following anticholinesterase exposure can be demonstrated in the monkey, then it deserves more research for applicability of verifying field OP exposures by an atropine challenge and monitoring postexposure treatments.

Experiments II and IV demonstrated that the VTM parameters may be useful in contrasting central vs. peripheral nervous system (PNS) effects. The overall rate parameters of HR, HP, and HPV are influenced by peripheral nonneural mechanisms as well as sympathetic neurally mediated factors (e.g., vasomotor and baroreceptors). The HPV parameter is mediated by both CNS and PNS factors; however, V may be more specifically mediated by central vagal efferent activity.

Atropine sulfate is known for its central anticholinergic activity, and the VTM parameters reflected this activity by strong treatment effects for HPV and V in contrast to the weak HR and HP effects. In addition, pyridostigmine, a quaternary carbamate that does not easily cross the blood brain barrier, consistently affected the more peripheral measures (HR, HP, and HPV) but not V. This phenomenon can be contrasted nicely with the more central effects of physostigmine which produced treatment interactions for V, but not for HR and HP.

The response of the VTM parameters to the carbamates indicates a potential problem with using the device for monitoring anti-ChE exposures. The centrally active compounds may directly affect V while the nonlipophilic and peripherally active compounds may not show any reliable effects. Figure 18 clearly shows that the 25-µg dose of physostigmine resulted in increased V while the 100-µg dose resulted in decreased V in contrast to pyridostigmine which produced little, if any, effect. This phenomenon can be explained by the complex non-cholinesterase effects of many anti-ChE compounds including: (1) direct muscarinic receptor antagonism, (2) reflexive response to autonomic ganglion overstimulation due to nicotinic agonistic activity, or (3) reflexive response to reduced peripheral blood pressure resulting in reduced vagal output. The nerve agents tend to be highly lipophilic and the VTM may, therefore, be useful for directly monitoring their effects at higher doses. Because one area of military interest regarding the dose-response relationship of these compounds is that of subtle effects, the increase in V may be more useful as a direct measure of exposure.

Experiment III provides perhaps the most exciting data for future applications of the VTM, because it validates the attenuated response of V to atropine sulfate following anticholinesterase (pyridostigmine) pretreatment. From this experiment we conclude that the V responses to 14-, 44-,and 140-µg atropine treatments were attenuated by pretreatment with pyridostigmine. Therefore, similar to the 2 dog studies (3,37), the V parameter may be used to verify that an anticholinesterase exposure has occurred even though no salivation, lacrimation, urination, defecation (SLUD) symptoms are present. Although ChE assays may be used for the same purpose, the VTM monitoring is noninvasive and provides an estimate of the status of the nervous system and, according to our other experiments, may accurately reflect the status of the CNS at the level of the brainstem. This monitoring is more important when one considers that some investigators now believe that death from OP toxicosis may be the result of central respiratory depression and not peripheral effects (41).

Furthermore, the treatment of nerve agent casualties will necessitate the use of atropine sulfate. The V response to atropine may be used to determine when a person is ready to return to service after a sub-lethal OP exposure.

Therefore, we strongly believe that the VTM should be studied further to determine its potential for use in military applications. We suggest that the next series of studies should include orally administered pyridostigmine plus OP administration. The studies should include pharmacokinetic monitoring of toxicants in the cerebrospinal fluid and blood to provide more evidence of the site of V responses.

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APPENDIX A

ANOVAS FOR VAGAL TONE MONITORING VARIABLES
FOLLOWING ATROPINE SULFATE (EXPERIMENT I),
USING ALL ANIMALS

Number of Observations in Data Set = 557

General Linear Models Procedures SAS

Dependent Variable: Heart Rate

Source	DF	Sum of Squares	F-Value	PR > F
Model	311	347787.17	5.45	0.0001
Error	251	51497.67		
Corrected Total	562	399284.84		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	126735.45	77.21	0.0001
Animal*Dose (Group)	24	60480.50	12.28	0.0001
Animal*Time (Group)	88	25282.06	1.40	0.0230
Dose*Time	33	12318.10	1.82	0.0050

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	23826.84	0.50	0.6918

Tests of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	22010.79	2.91	0.0551
Week	3	19969.48	2.64	0.0724
Group*Dose	6	4180.78	0.28	0.9425

Tests of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	11	13589.26	4.30	0.0001
Group*Time	33	7002.59	0.74	0.8355

Dependent Variable: Heart Period

Source	DF	Sum of Squares	F-Value	PR > F
Model	311	1740329.53	4.20	0.0001
Error	249	331981.19		
Corrected Total	560	2072310.72		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	545021.96	51.10	0.0001
Animal*Dose (Group)	24	358563.24	11.21	0.0001
Animal*Time (Group)	88	144565.52	1.23	0.1080
Dose*Time	33	54328.72	1.23	0.1860

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	101108.96	0.49	0.6959

Tests of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	84583.20	1.89	0.1587
Week	3	98357.60	2.19	0.1148
Group*Dose	6	11056.32	0.12	0.9924

Tests of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	11	70655.31	3.91	0.0001
Group*Time	33	54721.85	1.01	0.4696

Dependent Variable: Heart Period Variance

Source	DF	Sum of Squares	F-Value	PR > F
Model	311	814.62	4.73	0.0001
Error	247	136.88		
Corrected Total	558	951.50		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	115.68	26.09	0.0001
Animal*Dose (Group)	24	97.85	7.36	0.0001
Animal*Time (Group)	88	53.30	1.09	0.2950
Dose*Time	33	33.97	1.86	0.0040

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	56.74	1.31	0.3372

Tests of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	308.64	25.23	0.0001
Week	3	20.68	1.69	0.1957
Group*Dose	6	10.30	0.42	0.8576

Tests of hypotheses using the MS for Animal*Time(Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	11	36.28	5.45	0.0001
Group*Time	33	10.96	0.55	0.9730

Dependent Variable: Vagal Tone

Source	DF	Sum of Squares	F-Value	PR > F
Model	311	1175.77	6.11	0.0001
Error	247	152.93		
Corrected Total	558	1328.70		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	282.23	56.98	0.0001
Animal*Dose (Group)	24	201.81	13.58	0.0001
Animal*Time (Group)	88	70.97	1.30	0.0590
Dose*Time	33	29.15	1.43	0.0690

Test of hypotheses using the MS for Animal(Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	69.03	0.65	0.6036

Tests of hypotheses using the MS for Animal*Dose(Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	358.15	14.20	0.0001
Week	3	12.62	0.50	0.6857
Group*Dose	6	22.98	0.46	0.8340

Tests of hypotheses using the MS for Animal*Time(Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	11	26.11	2.94	0.0023
Group*Time	33	14.52	0.55	0.9741

FIFTEEN-MINUTE MEANS OF VAGAL TONE VARIABLES
BY ATROPINE SULFATE TREATMENT AND BY ANIMAL
(EXPERIMENT I)

Response variable=HR Atropine Sulfate Dosage=0

TIME	C02	C04	C06	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	176.250	127.407	134.684	222.571	184.000	128.471	138.400	162.514	210.588	132.607	146.800	200.100	163.699	9.8677	12
15	186.667	106.917	162.480	209.600	161.600	117.500	127.500	169.154	192.483	119.103	136.923	188.947	156.573	9.8862	12
30	154.000	66.615	157.000	203.455	162.696	115.630	126.071	172.370	185.586	122.200	145.667	195.000	150.524	11.1364	12
45	157.368	120.320	167.310	213.600	177.143	135.083	149.789	180.105	188.000	148.556	173.733	214.000	168.751	8.2718	12
60	154.571	132.414	140.429	214.667	185.200	122.417	136.917	173.364	184.200	143.241	163.800	203.000	162.852	8.5073	12
75	152.957	137.357	140.143	205.500	176.125	136.111	144.625	176.190	186.071	146.414	164.933	197.429	163.655	7.0094	12
90	151.185	124.828	133.750	198.200	184.833	142.000	140.889	178.750	186.593	149.647	175.071	192.333	163.173	7.3271	12
105	147.750	124.923	129.600	200.000	196.000	136.778	151.625	178.545	182.733	146.174	171.739	196.000	163.489	7.8575	12
120	147.917	122.000	125.630	201.200	179.556	138.333	142.200	183.667	179.259	148.267	151.400	197.333	159.730	7.8687	12
135	153.200	124.519	126.267	197.500	179.867	153.222	146.286	178.609	178.897	159.385	154.067	.	159.256	6.8827	11
150	148.880	121.120	129.273	189.846	181.882	148.000	155.143	176.000	175.400	162.800	171.034	197.500	163.073	6.7602	12
165	150.348	122.333	120.733	198.857	184.769	152.824	145.565	169.200	181.200	147.867	165.800	206.000	162.125	7.8883	12
180	158.889	129.111	129.000	.	178.857	148.824	153.818	168.000	183.800	144.700	163.000	196.000	159.454	6.4676	11

Response variable=HR Atropine Sulfate Dosage=0.014

TIME	C02	C04	C06	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	197.057	178.909	166.311	205.571	169.545	151.696	117.824	143.474	165.927	134.109	171.393	207.625	167.453	8.02277	12
15	197.840	140.154	156.714	200.167	201.250	144.261	116.333	156.588	154.207	125.931	154.800	184.720	161.080	8.31936	12
30	194.207	149.333	160.000	210.667	212.000	168.138	155.667	169.500	169.400	147.931	164.207	232.125	177.765	7.97584	12
45	161.200	177.182	178.345	215.455	217.500	165.524	171.333	216.000	198.138	162.571	158.500	214.200	186.329	6.95877	12
60	177.667	184.111	169.538	209.000	199.200	162.476	130.400	184.714	193.333	159.636	169.304	213.500	179.407	6.71711	12
75	172.929	176.000	163.429	207.500	210.000	160.261	138.667	187.500	199.448	161.769	162.320	228.286	180.676	7.53799	12
90	152.714	177.667	156.000	204.750	206.800	159.091	141.379	151.840	197.533	160.500	156.214	190.400	171.241	6.63975	12
105	167.517	178.111	150.276	201.833	193.222	166.778	156.000	157.778	203.200	159.714	152.000	217.750	175.348	6.65050	12
120	171.714	174.800	150.296	206.857	202.200	168.000	158.462	182.000	201.571	159.810	150.750	207.750	177.851	6.30490	12
135	174.867	187.167	139.034	206.500	194.182	171.529	141.407	187.385	208.533	165.048	147.692	186.286	175.803	6.84489	12
150	168.091	169.684	146.720	206.500	188.900	166.667	139.385	180.333	202.966	159.704	140.000	199.667	172.385	6.85066	12
165	.	166.500	133.214	222.000	188.300	171.600	123.818	184.100	202.600	157.692	140.667	.	169.049	9.89057	10
180	.	162.100	146.640	196.500	198.909	169.524	130.769	186.000	207.500	159.667	133.913	.	169.152	8.65992	10

Response variable=HR Atropine Sulfate Dosage=0.044

TIME	C02	C04	C06	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	181.378	178.839	169.250	165.000	152.069	143.725	169.684	167.542	204.302	144.667	104.192	184.333	163.748	7.3529	12
15	188.769	144.300	174.957	185.000	158.000	156.759	196.000	184.381	201.478	142.385	91.172	193.714	168.076	9.1078	12
30	167.467	177.500	198.357	198.100	188.182	174.909	233.333	183.407	218.333	159.800	119.667	215.176	186.186	8.7354	12
45	205.500	178.545	212.000	190.706	218.000	193.931	188.600	193.680	221.643	188.632	158.476	220.000	197.476	5.4336	12
60	180.148	170.000	187.000	182.696	200.000	171.364	177.231	187.357	186.889	189.529	135.286	188.000	179.625	4.6812	12
75	156.714	167.158	184.900	182.000	142.000	167.733	183.143	186.640	180.414	179.250	134.067	185.714	170.811	5.1593	12
90	169.643	164.182	201.667	173.391	200.000	158.417	183.091	180.615	194.667	195.294	139.600	.	178.233	5.8723	11
105	162.467	164.000	186.471	181.412	.	92.667	183.231	180.000	198.733	175.556	137.267	174.000	166.891	8.8356	11
120	164.000	163.647	179.667	181.259	80.000	174.533	191.600	200.667	202.000	171.158	142.333	206.000	171.405	9.8808	12
135	166.087	163.440	188.571	170.643	192.941	173.067	176.667	177.130	196.538	167.778	142.000	.	174.078	4.6171	11
150	165.267	155.789	184.167	174.100	183.000	178.353	174.933	185.467	191.867	165.231	131.267	.	171.767	5.1443	11
165	167.500	163.833	.	166.000	186.222	178.200	177.600	182.364	206.435	161.333	144.690	192.000	175.107	5.0826	11
180	165.714	157.304	179.310	173.200	152.160	328.000	174.182	177.500	228.929	161.304	154.880	.	186.589	15.4866	11

Response variable=HR Atropine Sulfate Dosage=0.14

TIME	C02	C04	C06	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	165.490	118.741	153.532	171.739	173.556	138.182	143.739	134.087	171.673	131.565	122.955	208.121	152.782	7.54549	12
15	189.000	147.667	144.889	190.588	225.000	169.037	197.333	137.778	203.462	166.370	155.481	214.720	178.444	8.35458	12
30	184.952	167.680	159.000	191.158	230.000	166.696	186.000	162.800	200.333	180.400	156.400	217.185	183.550	6.71537	12
45	198.353	171.571	192.556	187.333	226.000	188.300	176.000	194.353	207.533	185.462	203.167	181.600	192.686	4.28373	12
60	180.923	154.643	164.400	198.909	206.769	173.407	178.400	157.913	199.600	181.273	160.533	198.917	179.641	5.23408	12
75	182.933	144.080	154.000	207.800	207.000	163.238	179.400	166.095	204.200	209.000	151.400	192.333	180.123	6.93470	12
90	177.929	132.828	149.571	191.263	198.737	159.789	178.500	162.286	196.533	192.700	148.667	205.739	174.545	6.78664	12
105	177.200	135.586	139.125	194.800	200.667	162.167	178.500	164.000	195.733	199.556	160.400	153.200	171.744	6.62189	12
120	177.840	135.040	141.500	188.889	205.882	162.000	179.231	164.400	187.067	206.500	148.867	201.000	174.851	7.10822	12
135	173.000	131.130	137.417	195.778	177.846	164.889	186.800	168.125	192.067	178.533	145.133	204.000	171.227	6.70567	12
150	172.545	122.154	136.815	178.000	197.111	160.556	168.471	113.304	193.667	191.167	143.867	202.286	164.995	8.67547	12
165	173.923	124.000	139.333	180.875	194.909	165.308	190.333	162.923	188.966	179.407	143.800	184.667	169.037	6.53355	12
180	174.800	123.154	131.263	179.478	194.222	159.862	176.000	165.000	200.083	178.286	146.000	.	166.195	7.35398	11

Response variable=HPER Atropine Sulfate Dosage=0

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	343.400	471.667	445.395	276.476	327.448	469.745	434.886	377.457	284.882	454.500	409.600	299.600	382.921	21.3921	12
15	330.000	441.875	371.320	286.000	373.200	513.893	470.333	358.000	311.517	504.069	438.308	317.947	393.039	22.5548	12
30	390.000	210.923	384.000	295.727	369.609	521.519	475.679	347.926	322.897	491.067	411.767	309.063	377.515	25.7740	12
45	381.158	500.040	367.207	281.800	339.714	458.957	403.316	336.263	318.963	405.500	347.300	282.000	368.518	19.0690	12
60	387.714	456.069	427.357	279.333	324.000	490.833	438.500	346.455	325.467	418.966	366.500	296.750	379.829	19.4225	12
75	392.043	439.821	428.556	292.000	341.125	442.222	415.375	342.000	322.107	410.655	363.933	303.714	374.463	15.5467	12
90	396.889	482.069	449.042	303.000	324.917	423.875	426.444	337.833	321.704	413.235	344.536	311.667	377.934	17.5535	12
105	406.625	481.269	463.000	303.700	305.800	441.412	396.063	336.273	327.967	410.913	353.087	305.800	377.659	18.4533	12
120	405.250	492.750	477.519	298.400	335.444	434.367	422.100	329.647	334.741	404.800	396.433	303.833	386.274	18.8756	12
135	391.600	483.259	477.067	303.625	333.733	426.353	410.095	337.304	335.448	378.769	389.400	.	387.878	17.7000	11
150	402.880	497.280	464.545	316.615	330.176	406.526	387.810	344.267	342.033	382.600	351.724	303.500	377.496	16.9653	12
165	398.783	493.200	497.100	302.500	325.231	393.353	412.000	358.000	330.800	405.933	362.633	292.000	380.961	19.2077	12
180	378.778	465.852	466.917	.	336.286	404.118	392.318	359.000	326.100	414.900	368.500	307.000	383.615	15.7977	11

Response variable=HPER Atropine Sulfate Dosage=0.014

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	304.358	341.591	360.978	291.857	354.818	397.043	509.382	420.053	362.073	450.036	351.804	288.906	369.408	18.9836	12
15	303.040	428.423	383.893	300.167	298.250	418.913	519.083	383.647	389.207	477.931	387.560	325.560	384.639	20.3471	12
30	308.655	402.700	377.923	284.000	282.813	357.793	385.583	353.667	355.067	407.172	365.172	270.667	345.934	13.7887	12
45	372.120	339.273	341.897	278.273	276.250	365.048	351.417	278.750	303.759	369.857	379.429	279.444	327.960	12.0310	12
60	337.533	325.389	354.962	287.111	302.000	370.429	461.300	324.857	310.667	377.727	354.304	281.000	340.607	14.1738	12
75	347.429	340.750	368.071	288.875	286.000	375.000	432.233	320.250	300.655	373.346	369.560	273.000	339.597	13.6283	12
90	394.000	337.417	385.615	293.000	290.600	377.727	424.379	442.840	303.300	374.600	384.107	315.200	360.232	14.8131	12
105	359.000	336.500	400.759	297.000	310.353	360.167	385.526	412.889	295.267	377.571	395.520	280.750	350.942	13.2442	12
120	349.464	343.200	400.667	290.143	297.200	358.818	379.192	331.200	297.571	376.286	398.583	301.250	343.631	11.6637	12
135	343.200	330.750	432.034	290.250	309.182	350.412	425.333	321.077	287.600	365.190	406.885	329.615	349.294	14.2128	12
150	357.227	354.833	411.240	290.188	317.700	361.048	433.462	332.833	295.483	376.074	428.889	311.167	355.845	14.2496	12
165	.	361.364	450.893	286.750	319.300	351.200	484.500	326.900	295.900	380.654	426.917	.	368.438	21.1503	10
180	.	372.737	413.120	304.938	301.727	354.524	458.846	323.526	289.000	377.333	449.261	.	364.501	19.3359	10

Response variable=HPER Atropine Sulfate Dosage=0.044

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	332.156	340.258	356.766	363.857	402.345	418.608	354.278	359.000	294.491	415.463	577.673	325.750	378.387	21.0190	12
15	317.808	417.700	344.522	325.800	381.750	384.828	306.857	325.810	298.261	426.846	659.172	310.500	374.988	28.7545	12
30	360.433	339.000	303.000	303.526	318.818	343.500	271.667	326.815	274.333	375.250	503.933	278.412	333.224	18.2767	12
45	292.125	336.000	283.250	315.118	268.500	311.621	317.600	311.120	271.000	317.947	385.905	272.778	306.914	9.5893	12
60	332.778	352.857	320.813	328.652	300.167	352.182	338.692	320.107	321.167	327.353	443.393	318.000	338.013	10.4766	12
75	383.214	358.789	324.350	330.750	526.333	358.333	326.692	321.920	332.552	335.125	447.700	323.857	364.135	18.0615	12
90	353.643	365.500	307.500	346.826	.	391.875	327.364	332.654	308.133	319.412	430.833	.	348.374	12.3974	10
105	369.067	365.667	321.882	331.412	.	668.500	327.231	332.857	301.533	342.667	438.900	339.000	376.247	31.1665	11
120	366.107	367.294	333.875	332.296	748.000	346.400	317.800	317.600	296.767	350.842	422.267	291.000	374.187	35.4787	12
135	361.130	367.120	322.071	351.857	311.000	347.533	339.111	339.391	305.192	357.389	423.133	.	347.721	9.6824	11
150	363.267	386.842	326.000	345.550	328.500	343.118	342.733	324.467	312.467	363.385	459.233	.	354.142	12.3121	11
165	358.286	366.583	.	361.773	321.611	338.400	338.100	331.045	290.304	371.476	415.552	311.500	345.876	10.2428	11
180	361.714	382.000	334.828	348.267	431.200	.	343.818	338.083	261.821	372.739	392.600	.	356.707	14.0734	10

Response variable=HPER Atropine Sulfate Dosage=0.14

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	363.725	481.556	394.128	349.391	345.861	435.909	421.364	448.043	351.327	456.087	488.727	287.970	402.007	18.1404	12
15	317.000	413.125	415.111	314.941	266.375	355.185	304.333	438.667	294.423	361.519	386.370	279.120	345.514	16.7052	12
30	324.524	357.400	378.727	313.895	260.857	360.000	322.000	369.650	299.000	332.800	383.300	275.778	331.494	11.4991	12
45	305.438	349.929	315.778	320.333	265.000	321.650	340.857	309.176	289.367	325.846	295.625	330.000	314.083	6.7151	12
60	331.462	388.250	366.267	301.364	290.308	351.667	335.200	382.913	300.467	331.773	374.133	301.125	337.911	10.0409	12
75	327.867	417.200	390.130	289.000	289.500	370.095	334.000	363.952	293.500	289.625	396.033	312.000	339.409	13.4576	12
90	336.929	451.310	402.071	313.632	301.842	375.579	335.250	371.786	305.500	313.300	403.333	291.304	350.153	14.4994	12
105	338.233	443.276	430.938	306.222	298.889	370.250	335.833	370.118	306.567	300.333	376.167	271.400	345.685	15.5521	12
120	337.040	445.360	425.679	318.222	291.706	371.000	334.077	365.520	321.500	294.625	402.967	298.500	350.516	14.9912	12
135	347.000	459.217	439.792	308.833	362.385	364.278	321.067	359.938	312.833	336.133	413.667	293.500	359.887	15.2341	12
150	347.500	492.269	439.778	338.143	304.611	374.278	356.000	582.130	309.833	313.875	417.133	297.143	381.058	25.1754	12
165	345.423	484.920	438.143	333.750	308.182	364.192	326.417	370.846	317.793	334.259	417.533	335.333	364.733	15.7285	12
180	343.533	489.654	457.474	335.913	308.333	375.586	340.706	365.700	299.833	335.857	411.120	.	369.428	18.1704	11

Response variable=HPERVAR Atropine Sulfate Dosage=0

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	2.71250	6.32778	4.51053	1.94737	3.63929	4.87647	4.41429	4.12000	2.21569	4.93214	4.66735	3.93590	4.02494	0.360231	12
15	5.33333	7.32500	4.10000	4.36000	4.62857	5.95714	4.81250	4.34615	3.28621	5.93793	5.25000	5.01667	5.02946	0.303043	12
30	4.61429	8.12692	4.38571	3.34545	5.03182	6.38519	5.53571	3.49630	3.91379	5.67333	5.28333	4.80000	5.04932	0.381717	12
45	3.50526	6.90000	4.48966	4.26000	4.47857	5.35652	4.42778	3.68947	4.04074	5.36471	5.03667	6.00000	4.79578	0.284049	12
60	3.68214	6.37241	4.33571	4.03333	3.74000	5.80000	4.84583	4.23810	3.92000	4.22069	5.08000	6.30000	4.71402	0.279563	12
75	3.77391	5.40000	4.40370	3.80000	4.60000	5.61111	5.14375	4.42381	3.97857	4.70345	4.95667	5.10000	4.65791	0.175893	12
90	4.24815	6.44138	4.98333	2.95556	4.38182	5.00000	5.17778	4.04167	3.96296	5.51250	4.53214	4.51667	4.64616	0.252911	12
105	4.31875	6.51154	5.13333	3.26000	3.84000	5.21765	5.31250	4.04091	3.97667	5.42273	4.63913	3.96000	4.63610	0.261890	12
120	3.90000	6.38571	5.29259	3.92500	4.25556	4.90667	5.12000	4.00588	4.28462	5.43333	5.51333	4.50000	4.79356	0.224261	12
135	3.59600	6.21154	5.49667	3.70000	4.76000	4.81176	4.83333	4.21739	4.47931	5.30769	5.23000	.	4.78579	0.233996	11
150	4.14000	6.18000	4.83182	3.65000	4.10000	4.51111	4.72857	3.92857	4.52000	5.06000	5.15172	4.75000	4.62932	0.193141	12
165	4.19565	6.39333	5.66000	3.64615	4.06923	4.35294	4.83043	4.54667	4.32333	4.95333	5.29667	6.50000	4.89731	0.261807	12
180	3.66538	6.29259	5.11667	.	4.43810	4.74706	5.01364	5.20000	4.04500	4.82000	5.12500	3.90000	4.76031	0.222048	11

Response variable=HPERVAR Atropine Sulfate Dosage=0.014

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	2.34340	3.63488	4.17778	3.37143	3.66818	4.45333	5.92647	4.65676	3.17273	4.53818	3.24107	3.60333	3.89896	0.266109	12
15	1.32800	6.21154	4.16786	3.47500	2.28333	5.50909	5.98333	4.26250	4.40345	5.00690	2.97200	4.57200	4.18125	0.423973	12
30	1.43448	5.48333	3.95385	2.00000	2.80625	4.08276	3.65417	3.59091	3.49333	4.89655	2.08276	3.08000	3.37987	0.342352	12
45	3.33200	4.12273	3.25172	1.92727	2.95000	3.85789	3.02500	4.10000	2.76552	4.55714	2.78214	2.80000	3.28929	0.214915	12
60	3.24667	2.00000	3.42308	2.08889	3.62500	4.50476	4.52333	3.69286	2.35667	4.71818	2.43478	4.83333	3.45396	0.302754	12
75	3.31429	3.98571	3.37857	1.96250	.	4.56522	4.40667	2.70000	1.98276	4.86538	2.56000	5.90000	3.60192	0.380686	11
90	4.38929	3.37500	3.60769	2.04667	3.72500	4.70909	4.62414	3.72800	2.40667	4.51579	2.45714	5.00000	3.71537	0.285596	12
105	3.77931	3.55556	3.90690	2.36667	3.51765	4.45000	3.50000	3.60000	2.05667	4.62381	3.42800	5.38571	3.68086	0.260516	12
120	3.46786	3.44667	4.45926	2.38571	3.64000	4.17143	3.06538	3.72000	2.85000	4.77143	3.10417	5.37500	3.70474	0.247437	12
135	3.80000	3.75000	4.62759	2.38333	4.07273	4.43125	4.09630	3.76154	1.78333	5.09524	3.22308	4.60769	3.80267	0.275051	12
150	3.42727	4.12222	4.68000	1.97500	4.10000	4.65238	4.31923	4.14167	2.46552	4.74815	3.48519	5.79167	3.99236	0.299650	12
165	.	4.13636	4.57500	2.32500	3.96316	4.82667	5.73182	3.28421	2.07667	5.36538	4.13750	.	4.04218	0.378825	10
180	.	4.56842	4.90800	2.29375	3.89091	4.15238	5.58846	4.06316	2.10000	5.31667	4.12609	.	4.10078	0.363304	10

Response variable=HPERVAR Atropine Sulfate Dosage=0.044

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	3.38222	3.89355	3.37447	4.60714	3.9690	4.23137	3.27222	3.08125	2.73396	4.28519	6.57500	5.42609	4.06929	0.312275	12
15	1.75200	4.88000	2.68261	2.07500	4.7937	3.05517	1.78000	1.94762	2.66957	4.68800	7.66207	4.12857	3.50953	0.512838	12
30	2.50667	3.00000	2.79643	2.53158	2.8636	2.87273	1.05000	1.14815	1.20667	3.41500	4.72333	0.90588	2.41834	0.330913	12
45	1.70000	2.85000	1.65000	2.20588	3.2000	2.50690	1.61000	1.83600	1.50357	3.54737	3.64762	3.05556	2.44274	0.229801	12
60	1.36667	2.97857	2.63750	2.46364	1.6400	3.55909	1.66667	1.98929	2.91667	3.52667	3.74286	5.56667	2.83786	0.338863	12
75	3.10357	3.09474	3.26500	1.95000	3.6667	3.56667	1.81538	2.00400	2.27931	2.80000	3.97667	4.30000	2.98517	0.239221	12
90	2.64444	3.22273	3.10909	2.57826	.	3.92083	1.78182	2.43846	1.91667	3.35294	3.96000	.	2.89252	0.238451	10
105	2.34667	3.21667	2.58824	2.48824	.	5.30000	1.92308	2.73929	1.78667	3.37647	4.21333	.	2.99786	0.341712	10
120	3.60714	3.44706	2.54348	2.82222	10.1000	4.08667	2.26667	2.79333	2.19000	2.78947	3.70000	5.50000	3.82050	0.629704	12
135	2.66087	3.66000	3.84286	3.04286	2.9625	3.89333	3.50000	3.15652	2.41154	3.86471	4.71333	.	3.42805	0.198880	11
150	3.52000	4.17895	3.08333	2.90500	3.1875	3.86250	3.02667	2.78000	2.91333	3.69231	4.73000	.	3.44360	0.186342	11
165	2.79286	4.74167	.	3.26190	3.4778	4.01000	3.04000	3.11818	2.13043	3.45238	4.10690	2.60000	3.33928	0.223375	11
180	2.56786	4.44348	3.09310	3.29286	4.3000	.	3.46000	3.40833	1.98571	3.68696	3.80400	.	3.40423	0.234431	10

Response variable=HPERVAR Atropine Sulfate Dosage=0.14

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	3.94510	7.02963	4.12128	4.66364	3.72500	4.35091	4.06364	4.71739	3.74727	4.40652	4.82500	3.28710	4.40687	0.272276	12
15	1.56667	3.27083	3.30000	2.47500	1.71250	2.14231	0.92000	4.66250	1.13846	2.98889	2.51111	1.55200	2.35336	0.310917	12
30	2.19524	2.08000	3.20455	2.11053	0.94000	2.33478	1.43333	2.79000	1.65333	2.84667	2.68333	0.46154	2.06111	0.235401	12
45	0.90000	2.67143	2.20556	2.63333	0.00000	2.01500	1.78333	3.11176	1.73000	2.26538	2.45000	4.44000	2.18382	0.317201	12
60	2.13077	3.33214	2.51333	2.44000	2.20833	2.93077	2.12500	3.08261	1.73000	3.03636	2.51667	0.98333	2.41911	0.188412	12
75	2.29000	3.38750	2.70870	2.55000	1.55000	3.20000	1.96000	3.44500	1.73667	3.91429	3.15000	1.41667	2.60907	0.238225	12
90	2.26429	3.27586	2.89286	2.01111	1.64211	3.25789	2.02500	3.69286	2.30000	2.59500	3.18667	0.92609	2.50581	0.230400	12
105	2.80667	4.21379	2.52500	2.21250	2.22222	3.69167	2.25000	3.01176	2.49000	3.01111	3.02000	7.55000	3.25039	0.428291	12
120	2.67917	4.32000	3.02500	2.28333	1.85625	3.32500	2.27692	2.94400	2.67667	2.60000	3.49667	3.00000	2.87358	0.187058	12
135	3.03000	4.97826	3.14583	2.44706	2.36154	3.38235	1.26429	3.92000	2.74000	3.02667	3.50667	3.12500	3.07731	0.260001	12
150	3.22273	5.43077	3.48846	2.68500	2.37778	3.88333	2.14118	4.65652	2.68333	2.43478	4.11000	2.78571	3.32497	0.293563	12
165	2.90769	5.79600	2.92381	2.88000	1.61000	3.35769	2.20909	4.00000	2.92069	2.74074	4.31333	6.05000	3.47575	0.388438	12
180	2.75862	6.20769	3.35789	3.27826	2.27778	3.88966	2.17059	4.27500	2.26250	3.61429	4.48400	.	3.50693	0.362772	11

Response variable=VAGTONE Atropine Sulfate Dosage=0

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	0.24250	5.62222	0.31316	0.342105	0.99286	2.85294	2.90000	0.23714	0.06275	3.10714	3.33265	1.28718	1.77439	0.508376	12
15	1.83333	6.65000	1.31600	0.420000	2.12857	5.10357	3.44583	0.37308	0.80690	5.35862	4.09615	2.78333	2.85962	0.602046	12
30	1.10000	7.41538	1.01429	0.000000	2.04091	5.51111	4.25357	0.00000	1.77241	4.86667	4.48000	2.69286	2.92893	0.680136	12
45	0.65789	6.42000	1.49655	0.280000	2.47857	4.08696	2.81111	0.32632	1.90000	4.01765	3.66333	4.45000	2.71570	0.545619	12
60	0.55714	5.36207	0.48929	0.000000	2.74000	4.70833	3.17500	0.11905	1.88000	1.87241	4.07500	4.10000	2.42319	0.544018	12
75	0.72609	4.22143	0.81481	0.000000	2.57500	4.57222	3.84375	0.20952	1.78214	2.32759	4.03333	3.62857	2.39454	0.481380	12
90	1.21111	5.68621	1.03333	0.000000	2.62727	3.87143	3.85000	0.32500	1.68519	2.92500	2.81786	2.78333	2.40131	0.473329	12
105	1.01875	5.88077	0.93000	0.000000	2.50000	3.52353	3.95000	0.33182	1.74000	3.33636	3.10870	3.20000	2.45999	0.494731	12
120	1.11250	5.80357	1.09630	0.000000	2.61111	2.95333	3.96500	0.84118	2.31154	3.05333	4.74667	2.80000	2.60788	0.488616	12
135	0.84000	5.63077	1.22333	0.000000	2.64667	3.15882	3.83810	0.58596	2.34828	3.14615	4.58667	.	2.54598	0.531845	11
150	0.88400	5.52800	1.03636	0.300000	2.77500	2.73889	3.45714	0.72857	2.57333	3.01000	3.41379	2.92500	2.44751	0.428151	12
165	1.41739	5.73667	1.27000	0.430769	2.71538	2.52941	3.74348	1.00667	2.27667	3.22000	3.76333	4.90000	2.75081	0.464135	12
180	0.46923	5.58889	1.53333	.	2.78095	2.48235	3.56818	0.70000	1.72000	3.03000	3.80000	3.30000	2.63390	0.448047	11

Response variable=VAGTONE Atropine Sulfate Dosage=0.014

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	0.07358	2.08372	1.19333	0.000000	1.62727	1.69778	5.22059	0.17568	1.06545	2.25636	0.61964	0.93000	1.41195	0.409538	12
15	0.00000	5.49231	0.98571	0.116667	0.00000	3.52273	4.48333	0.53125	2.82759	2.48276	0.31200	1.77200	1.87720	0.543927	12
30	0.00000	4.22333	0.39615	0.000000	0.31250	0.50000	1.42500	0.06364	0.59333	1.75862	0.00000	0.88000	0.84605	0.348214	12
45	0.08400	2.31364	0.18276	0.000000	0.41250	1.02632	0.83333	1.30000	0.13448	0.96190	0.46429	0.87778	0.71592	0.190300	12
60	0.08333	0.26667	0.14615	0.000000	0.00000	1.41905	2.29667	1.57857	0.00000	1.27273	0.00000	3.10000	0.84693	0.307754	12
75	0.52500	1.51429	0.05000	0.000000	.	1.77391	2.93000	0.23000	0.00000	1.58846	0.00000	3.52857	1.10366	0.380563	11
90	1.17500	0.86667	0.05385	0.000000	1.97500	2.09091	2.85862	0.27200	0.00000	1.44211	0.00000	3.00000	1.14451	0.325828	12
105	0.94483	0.58889	0.47586	0.000000	0.24706	1.96111	1.17368	0.60000	0.00000	2.08571	0.54000	2.81429	0.95262	0.257944	12
120	0.78571	0.81333	1.21852	0.000000	0.35000	1.72381	0.62308	0.34000	0.00000	1.82381	0.36667	3.08750	0.92770	0.261512	12
135	1.40667	1.96000	1.32069	0.000000	1.02727	1.84375	1.65926	0.28462	0.00000	2.11429	0.53846	2.86154	1.25138	0.261270	12
150	1.09091	1.89444	1.48800	0.000000	1.38500	2.27619	2.33846	1.34167	0.07931	2.27407	1.10370	3.56364	1.56962	0.287253	12
165	.	2.53636	1.52500	0.475000	1.67895	2.30667	4.65909	0.29474	0.00000	2.55000	1.26250	.	1.72883	0.436219	10
180	.	3.11053	2.02000	0.143750	1.75455	1.95238	4.35000	0.40000	0.00000	2.93333	1.80000	.	1.84645	0.440955	10

Response variable=VAGTONE Atropine Sulfate Dosage=0.044

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	0.577778	2.55161	0.627660	1.23929	1.22069	1.77843	1.40588	0.000000	0.554717	1.60926	5.57115	3.64348	1.73166	0.449158	12
15	0.208000	3.23000	0.121739	0.00000	1.38125	0.76897	0.00000	0.114286	0.704348	2.48800	6.98960	1.77143	1.48147	0.586112	12
30	0.036667	0.48667	0.000000	0.26316	0.00000	0.25000	0.00000	0.140741	0.000000	0.07000	2.19667	0.17647	0.30170	0.177501	12
45	0.000000	0.00000	0.000000	0.00000	0.00000	0.00000	0.00000	0.000000	0.000000	0.00000	0.53333	2.42222	0.24630	0.202703	12
60	0.066667	0.05000	0.000000	0.00000	0.36000	0.69091	0.00000	0.000000	0.127778	0.00000	1.09643	4.46667	0.57154	0.367873	12
75	0.235714	0.03684	0.230000	0.00000	1.86667	0.19000	0.00000	0.056000	0.000000	0.00000	0.69333	1.81429	0.42690	0.198839	12
90	0.000000	0.11364	0.063636	0.00000	.	0.56667	0.00000	0.026923	0.000000	0.14706	0.88000	.	0.17979	0.094960	10
105	0.106667	0.73333	0.252941	0.00000	.	1.46000	0.14615	0.000000	0.000000	0.00000	1.35667	.	0.40558	0.181406	10
120	0.164286	0.41765	0.100000	0.00000	7.00000	1.08000	0.00000	0.340000	0.086667	0.03684	0.90333	3.80000	1.16073	0.612933	12
135	0.078261	0.55600	0.521429	0.00000	0.00000	0.14000	1.17500	0.295652	0.026923	0.26471	1.55000	.	0.41891	0.154266	11
150	0.023333	2.72105	0.150000	0.00000	0.08750	0.28750	1.33333	0.106667	0.000000	0.24615	1.88333	.	0.62172	0.280622	11
165	0.000000	2.56667	.	0.00000	0.10000	0.28000	1.00000	0.404545	0.000000	0.11905	1.39310	0.55000	0.58303	0.240417	11
180	0.242857	2.75217	0.086207	0.00000	0.83600	.	1.37000	0.625000	0.000000	0.66087	1.02800	.	0.76011	0.265061	10

Response variable=VAGTONE Atropine Sulfate Dosage=0.14

TIME	C02	C04	C06	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	0.727451	6.53704	0.674468	0.190909	1.70278	1.90545	2.11818	0.34565	1.68000	2.75870	3.29545	0.93548	1.90596	0.503513	12
15	0.000000	0.88333	0.587500	0.000000	0.08750	0.17308	0.00000	3.17500	0.00000	0.11111	0.32222	0.38400	0.47698	0.257864	12
30	0.000000	0.00000	0.095455	0.000000	0.68000	0.29565	0.00000	0.37000	0.00000	0.00000	0.00000	0.04231	0.12362	0.062416	12
45	0.000000	0.05000	0.116667	0.000000	0.00000	0.19500	0.00000	1.54118	0.00000	0.11154	0.06667	2.70000	0.39842	0.243575	12
60	0.000000	0.18929	0.426667	0.000000	1.44167	0.30385	0.00000	0.33043	0.00000	0.19545	0.08333	0.30000	0.27256	0.114861	12
75	0.000000	0.44583	0.091304	0.000000	0.67500	0.03500	0.00000	0.21500	0.00000	1.00000	0.25000	0.00000	0.22601	0.093732	12
90	0.000000	1.72759	0.039286	0.000000	0.00000	0.07368	0.00000	0.71429	0.00000	0.00000	0.63667	0.00000	0.26596	0.152213	12
105	0.000000	2.29310	0.000000	0.000000	0.00000	0.05833	0.00000	0.77059	0.00000	0.00000	0.49333	5.30000	0.74295	0.456977	12
120	0.000000	2.56800	0.289286	0.000000	0.00000	0.07000	0.00000	0.81600	0.00000	0.15714	1.15000	0.00000	0.42087	0.223110	12
135	0.000000	3.47391	0.945833	0.000000	0.76154	0.20588	0.00000	0.60000	0.02333	0.00000	1.64000	1.10000	0.72921	0.294703	12
150	0.000000	4.71538	0.861538	0.000000	0.00000	0.29444	0.00000	1.12609	0.00000	0.00000	2.05333	0.81429	0.82209	0.399821	12
165	0.000000	4.54000	0.771429	0.000000	0.00000	0.42692	0.00000	0.66923	0.02414	0.07037	2.30333	2.80000	0.96712	0.424299	12
180	0.000000	5.14231	0.536842	0.395652	0.43333	0.72414	0.61765	0.96842	0.00000	0.00000	2.62800	.	1.04058	0.466273	11

APPENDIX C

ANOVAS FOR P-Q INTERVALS FOLLOWING ATROPINE SULFATE (EXPERIMENT I), USING ALL ANIMALS

Number of Observations in Data Set = 720

General Linear Models Procedure SAS

Dependent Variable: PQ intervals

Source	DF	Sum of Squares	F-Value	PR > F
Model	119	0.053047	18.37	0.0001
Error	489	0.011870		
Corrected Total	608	0.064916		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	0.009652	49.71	0.0001
Animal*Dose (Group)	24	0.005192	8.91	0.0001
Time*Animal (Group)	8	0.000215	1.10	0.3580
Dose*Time	3	0.000026	0.36	0.7800

Tests of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	0.002852	0.79	0.5336

Tests of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	0.003436	5.29	0.0060
Dose*Group	6	0.000901	0.69	0.6565
Week	3	0.000381	0.59	0.6294

Tests of hypotheses using the MS for Time*Animal(Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	1	0.000027	1.52	0.2533

APPENDIX D

ANOVAS FOR PLASMA AND ERYTHROCYTE CHOLINESTERASE PRIOR TO ATROPINE SULFATE (EXPERIMENT I), USING ALL ANIMALS

Number of Observations in Data Set = 100

General Linear Models Procedure SAS

Dependent Variable: Plasma Cholinesterase

Source	DF	Sum of Squares	F-Value	PR > F
Model	40	50.53	11.07	0.0001
Error	59	6.73		
Corrected Total	99	57.26		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Week)	26	5.92	1.99	0.0147

Tests of hypotheses using the MS for Animal (Week) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Animal	11	39.32	15.71	0.0001
Week	3	1.30	1.90	0.1542

Dependent Variable: Erythrocyte Cholinesterase

Source	DF	Sum of Squares	F-Value	PR > F
Model	38	100.32	9.93	0.0001
Error	73	19.40		
Corrected Total	111	119.72		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Week)	24	22.98	3.60	0.0001

Tests of hypotheses using the MS for Animal(Week) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Animal	11	67.11	6.37	0.0001
Week	3	1.74	0.61	0.6169

APPENDIX E

MEAN PLASMA ERYTHROCYTE CHOLINESTERASE ACTIVITY
DURING FOUR-WEEK PRELIMINARY PERIOD (EXPERIMENT I)

Plasma Cholinesterase Activity (mM/l/min)

Animal #	Week 1	2	3	4	Mean	SE	n
C02	2.21	2.57	2.05	2.25	2.34	0.13	9
C04	--	3.38	3.09	3.20	3.24	0.17	7
C06	--	0.91	0.88	0.88	0.89	0.02	6
OLX	1.62	1.94	1.78	--	1.81	0.11	11
OL3	1.47	1.54	1.73	--	1.65	0.17	6
OPW	2.17	3.28	3.97	2.65	3.05	0.24	9
005	2.13	2.19	2.27	1.55	2.06	0.12	10
OPE324	--	2.98	1.91	3.00	2.72	0.22	8
OPE352	--	1.83	1.72	1.57	1.72	0.09	7
N538	1.69	2.12	--	2.03	2.01	0.08	10
N584	1.74	1.73	1.77	1.28	1.63	0.08	8
N597	1.07	1.13	1.22	1.05	1.12	0.04	9
				Grand Mean	2.04	0.08	100

Erythrocyte Cholinesterase Activity (mM/l/min)

Animal #	Week 1	2	3	4	Mean	SE	n
C02	--	4.65	3.81	4.59	4.43	0.18	8
C04	--	5.06	5.59	6.00	5.42	0.18	8
C06	--	4.23	4.39	4.77	4.46	0.11	6
OLX	4.97	4.95	4.39	--	4.69	0.19	15
OL3	--	3.86	4.01	3.71	3.90	0.06	8
OPW	5.73	6.18	6.99	5.76	6.17	0.21	10
005	3.38	3.62	3.35	4.33	3.66	0.15	10
OPE324	--	4.03	4.16	4.15	4.09	0.16	8
OPE352	--	7.15	4.11	5.18	5.89	0.52	8
N538	5.30	5.54	--	5.33	5.46	0.21	11
N584	5.61	5.66	6.05	6.47	5.92	0.13	12
N597	--	4.98	5.66	6.27	5.47	0.21	8
				Grand Mean	5.00	0.10	112

APPENDIX F

ANOVAS FOR VAGAL TONE MONITORING VARIABLES
FOLLOWING PYRIDOSTIGMINE BROMIDE (EXPERIMENT II),
USING ALL ANIMALS, FOR THE FOUR EXPERIMENTAL WEEKS

NUMBER OF OBSERVATIONS IN DATA SET = 554

General Linear Models Procedures SAS

Dependent Variable: Heart Rate

Source	DF	Sum of Squares	F-Value	PR > F
Model	311	283670.78	6.38	0.0001
Error	242	34616.71		
Corrected Total	553	318278.49		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	124348.37	108.66	0.0001
Animal*Dose (Group)	24	25021.08	7.29	0.0001
Dose*Time	33	2712.44	0.57	0.9710
Animal*Time (Group)	88	15681.94	1.25	0.0970

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	39886.39	0.86	0.5021

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	12540.95	4.01	0.0191
Group*Dose	6	7701.27	1.23	0.3254
Week	3	3957.82	1.27	0.3086

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	11	20031.12	10.22	0.0001
Group*Time	33	8245.62	1.40	0.1079

Dependent Variable: Heart Period

Source	DF	Sum of Squares	F-Value	PR > F
Model	311	2873617.16	3.73	0.0001
Error	242	599654.14		
Corrected Total	553	3473271.30		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	1135160.35	57.26	0.0001
Animal*Dose (Group)	24	241903.76	4.07	0.0001
Dose*Time	33	168674.71	6.19	0.0001
Animal*Time (Group)	88	183185.69	0.84	0.8280

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	352567.35	0.83	0.5746

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	160117.41	5.30	0.0060
Group*Dose	6	88108.34	1.46	0.2349
Week	3	52752.45	1.74	0.1847

Test of hypotheses using the MS for Animal*Time(Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	11	168674.71	7.37	0.0001
Group*Time	33	88405.09	1.29	0.1763

Dependent Variable: Heart Period Variance

Source	DF	Sum of Squares	F-Value	PR > F
Model	311	355.53	5.05	0.0001
Error	242	54.75		
Corrected Total	553	410.28		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	179.36	99.11	0.0001
Animal*Dose (Group)	24	20.30	3.74	0.0001
Dose*Time	33	6.28	0.84	0.718
Animal*Time (Group)	88	26.89	1.35	0.038

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	13.92	0.21	0.8887

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	22.92	9.03	.0003
Group*Dose	6	15.18	2.99	.0251
Week	3	2.42	.96	.4297

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	11	20.37	6.06	0.0001
Group*Time	33	14.50	1.44	0.0920

Dependent Variable: Vagal Tone

Source	DF	Sum of Squares	F-Value	PR > F
Model	311	866.19	8.87	0.0001
Error	242	75.97		
Corrected Total	553	942.16		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	452.68	180.25	0.0001
Animal*Dose (Group)	24	75.19	9.98	0.0001
Dose*Time	33	15.42	1.49	0.0480
Animal*Time (Group)	88	52.32	1.89	0.0001

Test of hypotheses using the MS for Animal (Group) as an error term.

Group	3	50.64	0.30	0.8258

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	22.99	2.45	0.0885
Group*Dose	6	62.14	3.31	0.0163
Week	3	2.23	0.24	0.8696

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	11	22.03	3.37	0.0006
Group*Time	33	35.07	1.79	0.0168

APPENDIX G

FIFTEEN-MINUTE MEANS OF VAGAL TONE VARIABLES BY PYRIDOSTIGMINE BROMIDE TREATMENT AND BY ANIMAL (EXPERIMENT II)

Response variable=HR Pyridostigmine Dosage=ctrl

TIME	C02	C04	C06	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	190.359	143.234	164.348	159.765	162.316	211.208	145.231	94.320	148.679	134.333	129.965	121.500	151.271	8.87758	12
15	185.905	143.571	170.385	165.882	178.000	173.048	124.571	115.600	125.920	123.100	129.286	136.500	147.647	7.27792	12
30	187.143	144.167	164.308	177.556	162.000	177.000	128.320	115.565	126.867	123.043	127.333	147.000	148.358	7.10242	12
45	180.417	154.923	172.417	168.588	189.667	183.077	134.900	123.478	145.467	126.750	135.931	176.000	157.635	6.81576	12
60	179.133	150.000	162.143	186.615	185.200	170.714	124.429	126.824	137.867	136.960	121.467	175.000	154.696	7.11797	12
75	177.077	153.273	159.692	195.200	201.667	167.379	123.818	119.583	133.733	140.080	122.933	169.200	155.303	8.06686	12
90	171.789	151.826	170.800	191.636	197.000	171.200	123.520	140.429	130.933	144.737	122.000	161.571	156.454	7.23258	12
105	167.000	149.000	159.071	180.727	167.667	173.517	123.810	127.000	139.133	160.500	125.800	161.538	152.897	5.66954	12
120	165.448	153.111	162.207	210.000	198.500	169.133	120.552	125.818	140.067	160.800	133.733	170.333	159.142	7.81321	12
135	159.826	152.667	161.429	.	187.600	171.100	128.333	126.609	143.862	158.167	137.867	170.714	154.379	5.70450	11
150	170.222	161.143	168.308	.	172.308	164.583	119.800	146.250	146.133	171.048	136.533	174.353	157.335	5.34729	11
165	161.917	152.000	160.769	.	166.880	182.867	128.154	148.833	144.933	165.474	136.200	168.667	156.063	4.77244	11
180	164.947	157.333	172.778	.	168.706	176.800	124.824	148.857	154.267	162.286	142.400	176.500	159.063	4.79099	11

Response variable=HR Pyridostigmine Dosage=high

TIME	C02	C04	C06	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	172.549	174.300	199.784	184.057	148.778	155.259	100.915	106.048	147.472	141.375	120.276	186.286	153.092	9.24163	12
15	152.889	149.250	168.700	172.600	140.154	111.619	109.714	94.300	113.786	117.214	105.643	169.800	133.806	8.14813	12
30	149.259	138.143	167.875	156.222	128.556	111.000	110.519	93.700	125.733	112.467	101.733	128.000	126.934	6.53398	12
45	158.222	146.714	167.478	181.765	135.407	123.280	104.400	93.920	143.652	139.200	116.621	145.667	138.027	7.34116	12
60	171.259	156.400	163.238	170.375	139.360	124.160	121.500	102.250	136.714	116.400	107.800	184.000	141.121	7.90708	12
75	157.034	136.000	174.077	193.846	141.143	122.214	123.067	101.429	164.200	139.733	105.467	144.667	141.906	7.88909	12
90	166.593	148.333	172.824	184.750	142.727	127.067	128.154	95.455	153.933	145.800	103.517	170.667	144.985	7.95676	12
105	157.267	144.286	167.130	187.429	145.091	128.933	134.417	92.000	155.931	141.333	117.467	.	142.844	7.66335	11
120	147.091	143.176	171.727	191.333	150.267	130.667	133.077	96.429	157.333	142.786	117.133	185.818	147.236	7.85427	12
135	150.600	144.133	168.273	182.667	170.000	136.741	126.750	100.500	164.069	140.000	118.133	192.000	149.489	7.82221	12
150	148.444	159.750	170.696	179.125	163.375	153.724	119.375	149.333	175.250	134.800	125.655	176.000	154.627	5.76397	12
165	155.071	158.316	164.500	176.429	156.828	156.160	86.462	.	144.414	147.478	122.533	185.250	150.313	8.06719	11
180	160.667	154.000	174.615	179.867	163.714	166.000	75.200	.	146.200	145.882	135.310	182.000	153.041	8.96268	11

Response variable=HR Pyridostigmine Dosage=low

TIME	C02	C04	C06	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	193.818	147.000	148.824	164.500	138.195	149.500	141.254	133.200	149.286	149.241	124.156	165.333	150.359	5.17976	12
15	178.583	144.400	127.556	150.933	149.867	129.778	136.200	142.000	138.643	139.455	116.143	155.333	142.408	4.55570	12
30	183.071	142.400	92.727	157.000	146.667	122.667	128.500	128.519	139.733	132.917	110.800	155.600	136.717	6.74788	12
45	.	140.800	136.333	173.818	149.846	130.080	126.952	147.600	169.533	142.091	135.172	170.000	147.475	5.01484	11
60	168.667	139.500	139.750	180.667	168.125	129.172	118.250	163.833	153.333	140.800	130.467	162.667	149.603	5.57441	12
75	.	140.222	141.172	185.000	167.500	136.571	120.783	142.609	172.333	141.529	123.467	.	147.119	6.65409	10
90	.	146.375	143.913	204.571	170.421	143.655	122.593	157.600	181.267	140.957	125.200	.	153.655	8.05210	10
105	157.333	146.000	145.167	171.222	170.000	147.931	123.125	156.333	193.250	140.769	126.846	.	152.543	6.12810	11
120	.	146.500	155.231	180.400	185.714	150.593	122.000	162.615	146.875	144.000	127.308	186.000	155.198	6.56622	11
135	.	151.600	162.500	184.000	168.857	152.400	124.909	169.467	170.533	148.074	132.800	.	156.514	5.75568	10
150	166.000	138.000	166.476	189.333	165.800	157.714	124.636	162.316	168.074	146.545	135.733	.	156.421	5.56888	11
165	.	156.000	153.667	192.333	154.824	165.600	125.789	159.067	145.920	145.167	137.154	188.000	156.684	5.98041	11
180	170.000	155.500	164.000	200.000	165.455	172.154	131.429	156.222	155.100	148.000	136.333	207.000	163.433	6.47842	12

Response variable=HR Pyridostigmine Dosage=mid

TIME	C02	C04	C06	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	190.872	158.533	141.400	171.722	157.619	155.085	141.754	134.622	134.241	128.635	127.395	166.333	150.684	5.6101	12
15	185.630	146.348	138.000	173.412	138.667	131.692	116.952	107.000	108.786	114.154	111.852	141.429	134.493	7.2856	12
30	175.929	136.667	136.000	155.182	144.400	119.862	113.077	137.462	114.133	112.600	118.467	136.667	133.370	5.5541	12
45	170.929	132.435	157.867	163.556	148.429	136.133	133.172	107.310	138.552	131.077	152.545	142.400	142.867	4.9508	12
60	180.276	132.133	179.636	166.824	156.533	128.714	106.083	114.714	128.533	117.400	147.250	142.000	141.675	7.1933	12
75	179.111	142.857	177.727	168.941	162.182	137.000	124.083	139.167	125.467	122.067	133.000	136.167	145.647	6.0099	12
90	164.828	143.586	167.310	192.500	190.500	141.600	117.250	133.750	134.333	127.800	142.600	140.615	149.723	6.9055	12
105	167.630	143.040	173.238	183.250	186.222	141.857	119.037	141.333	146.400	130.957	142.500	145.630	151.758	6.0496	12
120	164.600	141.333	160.320	200.000	182.800	145.692	117.000	141.500	164.733	135.478	144.800	143.862	153.510	6.4522	12
135	165.778	141.000	165.091	174.429	176.000	146.235	124.750	.	172.200	139.840	142.923	151.556	154.527	5.1392	11
150	163.400	141.462	166.000	200.000	178.333	148.250	124.000	.	177.600	140.095	82.933	145.200	151.570	9.4600	11
165	170.957	141.538	169.700	193.429	175.091	154.174	122.000	.	186.696	134.100	70.455	167.867	153.273	10.5934	11
180	171.933	137.895	173.357	194.333	158.000	158.000	128.769	.	160.333	133.765	70.727	167.120	150.385	9.8458	11

Response variable=HPER Pyridostigmine Dosage=ctrl

TIME	C02	C04	C06	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	315.103	392.043	365.130	376.647	369.974	284.583	413.769	636.490	404.696	449.250	462.860	386.550	404.758	25.4773	12
15	322.333	429.571	352.308	364.647	337.667	347.143	482.333	520.800	476.400	488.450	464.750	465.083	420.957	20.4680	12
30	320.643	416.583	365.462	341.000	372.000	339.433	468.040	523.174	473.133	488.000	471.600	407.000	415.506	19.6336	12
45	332.333	388.846	350.125	356.588	315.500	328.500	445.350	486.304	419.033	475.813	444.414	340.000	390.234	17.7035	12
60	334.567	400.762	370.679	322.385	324.400	351.179	482.214	478.706	435.667	439.520	494.733	344.500	398.276	18.8839	12
75	339.038	391.545	376.692	308.600	297.833	358.000	485.318	503.042	449.333	430.040	491.167	355.200	398.817	20.6745	12
90	348.895	395.261	351.720	313.364	305.500	350.133	487.200	433.929	458.633	420.684	492.267	371.071	394.055	18.5526	12
105	359.500	401.875	379.607	333.636	371.833	345.621	485.810	474.500	431.600	375.875	478.033	372.462	400.863	15.4594	12
120	362.828	391.556	370.345	284.000	302.500	354.533	498.069	477.727	428.500	373.000	449.167	354.500	387.227	18.8881	12
135	375.826	392.917	373.107	.	320.300	351.100	470.000	475.174	417.552	379.333	436.167	351.500	394.816	15.0006	11
150	353.000	371.143	358.577	.	348.462	364.792	501.800	504.750	410.933	351.476	439.633	343.941	395.319	18.3243	11
165	371.333	394.923	375.923	.	359.880	327.933	469.192	402.833	414.500	363.684	440.867	355.222	388.754	12.3726	11
180	364.000	380.667	349.111	.	356.176	339.133	482.471	403.905	389.700	369.500	422.333	340.000	381.545	12.8240	11

Response variable=HPER Pyridostigmine Dosage=high

TIME	C02	C04	C06	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	348.529	344.000	302.297	327.629	403.528	390.111	673.407	568.190	410.566	426.672	500.638	322.476	418.170	32.1829	12
15	393.370	403.625	356.000	350.150	428.923	541.000	548.714	639.400	529.250	514.929	568.857	355.400	469.135	28.5621	12
30	403.111	433.643	358.688	386.833	469.556	542.083	544.000	643.684	479.133	535.467	591.433	474.167	488.483	24.7678	12
45	379.333	410.357	358.348	332.471	443.222	492.200	574.920	639.160	425.087	438.360	517.759	410.500	451.810	25.9458	12
60	352.481	391.200	368.905	354.063	430.800	485.600	494.929	590.563	439.929	516.967	557.767	327.000	442.517	25.0480	12
75	383.069	443.000	344.654	311.077	424.821	490.643	488.067	594.190	369.300	430.933	569.700	477.333	443.899	24.7650	12
90	364.259	404.417	348.647	325.750	420.864	472.800	468.385	629.091	390.367	413.800	580.241	372.667	432.607	26.5575	12
105	383.700	415.905	359.826	320.286	413.545	465.867	446.000	667.200	385.345	425.370	525.767	.	437.165	28.2848	11
120	409.136	419.294	350.273	314.667	400.333	459.833	450.538	622.821	381.733	422.429	512.967	322.636	422.222	24.5646	12
135	401.000	416.467	357.500	328.778	353.167	438.926	473.375	602.833	366.690	428.714	509.400	314.000	415.904	23.9393	12
150	406.037	375.813	353.348	336.000	367.750	391.897	502.500	461.333	342.333	445.000	479.621	341.000	400.219	16.8411	12
165	389.107	379.000	365.786	342.571	383.690	385.000	764.423	.	416.690	407.087	491.900	324.000	422.659	36.5844	11
180	374.963	390.000	345.154	334.200	367.857	361.056	868.800	.	410 867	411.765	450.310	329.500	422.225	45.9953	11

Response variable=HPER Pyridostigmine Dosage=low

TIME	C02	C04	C06	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	309.295	408.200	402.882	367.300	435.878	403.231	426.136	454.180	403.786	404.948	485.344	364.333	405.459	13.0631	12
15	336.083	416.300	499.944	398.067	401.867	463.444	441.300	425.909	433.036	430.591	516.679	384.667	428.991	14.1796	12
30	328.071	421.300	708.227	384.000	409.500	489.333	466.450	467.074	431.067	451.667	541.300	387.000	457.082	27.8716	12
45	.	426.000	440.600	347.364	402.231	467.040	472.524	406.480	362.300	423.682	447.310	353.000	413.503	13.2527	11
60	355.333	429.250	429.625	335.444	358.500	465.345	507.500	367.583	392.400	425.950	460.300	369.000	408.019	15.3375	12
75	.	428.111	424.828	325.625	359.333	440.357	496.783	422.348	348.767	425.000	486.367	.	415.752	17.7373	10
90	.	410.125	417.174	295.143	354.474	417.966	489.852	388.200	331.233	426.913	479.200	.	401.028	19.3551	10
105	380.000	411.000	413.625	352.556	353.500	406.862	487.875	384.333	310.625	427.385	473.654	.	400.129	15.7529	11
120	.	410.125	388.077	335.600	325.429	398.963	492.000	368.846	409.481	416.357	471.115	324.000	394.545	16.5837	11
135	.	395.000	369.250	327.429	355.786	393.933	480.045	359.867	352.300	406.296	452.400	.	389.231	14.9621	10
150	361.000	462.846	360.667	318.833	363.650	380.929	481.636	374.368	358.407	411.500	442.000	.	392.349	15.2538	11
165	.	384.818	391.333	312.667	387.294	363.400	477.632	378.400	412.440	413.708	438.154	319.556	389.037	14.4205	11
180	354.000	385.000	366.000	300.000	363.636	350.385	456.357	384.037	387.300	406.462	440.917	290.000	373.674	14.1348	12

Response variable=HPER Pyridostigmine Dosage=mid

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	314.000	379.200	425.020	350.972	380.571	390.119	429.596	448.333	453.086	468.667	471.302	361.167	406.003	14.6263	12
15	323.593	410.304	436.786	347.529	436.733	456.538	513.095	637.250	552.429	527.923	539.741	424.464	467.199	25.9970	12
30	341.071	442.238	443.045	387.818	420.500	501.138	530.385	437.846	530.133	534.967	506.967	439.667	459.648	17.7975	12
45	351.321	453.391	380.333	368.778	404.286	448.467	457.517	633.586	450.517	464.192	395.409	421.000	435.733	21.0757	12
60	333.759	454.533	335.318	361.294	386.333	466.214	565.625	592.786	467.800	513.733	409.500	423.313	442.517	24.4153	12
75	335.852	419.000	338.727	356.882	370.182	439.538	484.417	433.792	478.367	494.267	454.545	440.250	420.485	16.3756	12
90	364.621	418.379	360.310	313.833	315.125	423.720	512.875	449.188	447.167	472.667	422.600	427.269	410.646	17.6058	12
105	359.889	419.880	347.857	328.688	322.778	423.786	504.296	425.208	412.733	461.261	420.375	412.519	403.272	15.6208	12
120	365.500	425.190	375.480	300.714	329.200	412.423	512.654	425.500	364.433	445.565	414.600	417.207	399.039	16.1974	12
135	363.074	425.818	364.318	344.500	340.625	410.706	483.458	.	348.367	429.360	420.538	395.222	393.272	13.6394	11
150	368.600	425.077	363.889	300.778	336.708	404.917	484.520	.	337.967	428.952	776.333	413.160	421.900	38.7472	11
165	352.348	424.615	355.250	313.286	342.455	390.130	491.455	.	321.261	448.300	850.773	358.467	422.576	45.9267	11
180	349.767	444.842	346.393	309.944	379.625	375.000	466.423	.	374.000	449.412	848.545	359.080	427.548	44.5796	11

Response variable=HPERVAR Pyridostigmine Dosage=ctrl

TIME	C02	C04	C06	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	3.77179	6.13191	3.65870	4.61053	3.78158	1.42708	4.57436	6.13800	4.35357	4.58958	5.35965	7.61667	4.66779	0.449791	12
15	4.14286	6.47143	3.51923	4.06111	4.30000	4.14762	5.99524	5.99500	5.36800	5.77500	5.33214	6.94167	5.17077	0.319060	12
30	3.99286	6.28333	4.80769	4.06667	5.60000	4.03000	5.96000	6.20000	5.08333	6.03043	5.21333	7.65000	5.40980	0.318059	12
45	4.37917	5.92308	3.34167	3.82353	3.81667	4.07308	5.88500	5.49130	5.20333	5.39375	5.51034	4.30000	4.76174	0.259973	12
60	4.82333	6.23333	3.72500	4.32308	4.48000	3.91786	5.97143	5.32941	4.75333	5.04400	5.76333	5.00000	4.94701	0.225992	12
75	4.84231	5.77273	5.15385	3.95000	4.00000	4.62414	6.15455	5.65000	4.96667	5.52800	5.82000	4.72000	5.09852	0.205218	12
90	4.98421	6.16522	4.20800	3.20000	4.35000	4.25667	6.00000	5.54286	4.93667	5.11579	5.85000	5.36429	4.99781	0.251775	12
105	5.26818	6.33750	5.12143	3.75000	4.30000	5.02069	5.93333	5.57273	4.72667	4.12500	5.42667	5.80769	5.11582	0.224307	12
120	5.29655	5.91111	4.87241	5.00000	3.52500	5.12000	5.92414	5.19091	4.60333	4.33000	4.87000	6.01667	5.05501	0.206619	12
135	5.43043	5.90833	4.87857	.	3.97000	4.84500	6.02083	5.40870	5.02069	3.81667	5.03667	5.54286	5.07989	0.212040	11
150	4.82963	5.90000	4.66154	.	4.13846	5.12917	5.98667	5.23750	4.49000	4.47619	4.89000	4.89412	4.96666	0.172890	11
165	5.12500	5.75385	5.05769	.	3.50000	3.92000	5.99615	3.24167	4.48000	4.63158	4.92333	5.05556	4.69862	0.261180	11
180	5.38421	5.90000	4.35556	.	3.88824	3.96333	5.71765	5.01429	4.39333	4.07857	4.66667	4.55000	4.71926	0.210250	11

Response variable=HPERVAR Pyridostigmine Dosage=high

TIME	C02	C04	C06	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	4.78235	5.29000	3.27568	3.74857	4.21389	3.99630	6.09661	5.78571	4.44717	4.30312	5.55345	4.48571	4.66488	0.248183	12
15	5.58519	6.07500	4.43000	4.60500	5.52308	6.23810	6.80952	5.01500	5.26786	6.26071	6.52143	5.75000	5.67341	0.215968	12
30	5.54444	5.83571	3.96250	5.02222	5.76111	6.28750	6.16296	6.50500	5.93333	6.21000	6.26667	8.36667	5.98818	0.294937	12
45	5.19630	5.95000	3.96957	4.10588	5.67407	5.91600	5.78400	4.76000	5.44783	5.53200	6.19310	6.25000	5.39823	0.219063	12
60	4.79630	6.12000	4.46190	4.33125	5.91200	6.24800	5.92857	5.30000	5.62500	6.05667	5.94000	4.86667	5.46553	0.198137	12
75	5.97241	6.20000	4.53846	4.84615	5.70000	6.23929	5.86667	5.06190	4.86667	5.64333	6.36333	6.21667	5.62624	0.183970	12
90	5.22593	6.34583	4.17647	4.23750	5.56364	6.27667	6.06923	5.57273	5.23000	5.36667	6.15517	5.41667	5.46971	0.205762	12
105	5.88333	6.10000	4.92609	4.95714	5.31364	6.23333	6.05833	5.51000	4.92069	5.32963	6.23000	.	5.58747	0.160361	11
120	6.23182	6.18235	4.54545	4.17778	5.03333	6.31250	6.06154	5.42500	4.66000	5.68214	5.89000	4.97273	5.43122	0.212696	12
135	5.99667	6.31333	5.26818	3.93333	4.10000	5.51852	6.46875	5.15000	4.78621	5.38571	5.91333	6.30000	5.42784	0.241658	12
150	5.96296	6.25625	4.93043	3.56875	4.30625	5.68621	6.52500	6.63333	4.44167	5.02000	5.75172	6.00000	5.42355	0.278373	12
165	5.70000	6.03684	5.28929	4.37143	4.56552	5.25200	7.36923	.	5.32414	4.85217	5.74667	4.88750	5.39953	0.249556	11
180	5.48889	6.08889	5.02308	4.19333	4.15714	4.82778	7.44800	.	4.83000	4.83529	5.42759	5.65000	5.27000	0.280716	11

Response variable=HPERVAR Pyridostigmine Dosage=low

TIME	C02	C04	C06	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	3.58636	6.41000	4.19118	3.68500	5.51220	4.56346	4.94068	5.32800	4.14286	3.61034	5.51719	5.43333	4.74338	0.264930	12
15	4.40000	6.55000	5.87222	3.82667	4.94667	5.68889	5.77500	4.58182	4.70357	5.27273	5.65357	6.43333	5.30871	0.240787	12
30	4.26429	6.52000	6.56364	4.55000	4.95556	5.88000	5.79500	5.12593	4.78333	5.75000	5.95667	6.03000	5.51453	0.219020	12
45	.	6.21000	5.65000	4.17273	5.01538	5.87600	5.94762	4.62800	4.93333	5.44545	5.42759	6.23333	5.41268	0.200192	11
60	5.10000	6.47500	5.83750	4.74444	4.15000	5.71379	5.47500	4.77500	4.72000	5.71500	5.23667	6.60000	5.37853	0.212253	12
75	.	6.41111	5.79310	4.65000	3.93333	5.61786	5.91739	5.10000	4.59667	5.68235	5.23667	.	5.29385	0.234158	10
90	.	6.28750	5.39565	4.72857	4.33158	5.18621	6.04444	5.08000	3.44000	5.71739	5.26000	.	5.14713	0.263859	10
105	3.43333	6.35000	5.36250	3.98889	3.74167	5.22759	6.05000	4.61667	2.77500	5.06923	5.12308	.	4.70345	0.334644	11
120	.	6.47500	4.83846	4.45000	3.97143	5.21111	5.63846	5.06154	4.76296	5.14286	5.32308	5.30000	5.10681	0.194554	11
135	.	6.10000	4.20833	4.30000	4.28571	5.33333	6.10000	4.52667	3.96000	5.22963	5.44000	.	4.94837	0.251294	10
150	3.80000	6.11538	4.28095	4.20000	4.13500	4.88571	6.15455	4.57368	4.29630	5.31818	5.42667	.	4.83513	0.244886	11
165	.	6.10000	4.50417	4.31667	4.65294	4.90400	5.96316	4.51333	5.14000	4.89167	5.36538	4.55556	4.99153	0.180367	11
180	4.90000	6.00000	4.45000	2.50000	3.77273	4.75769	6.12857	4.17407	4.30500	5.22692	5.32917	3.65000	4.59951	0.296749	12

Response variable=HPERVAR Pyridostigmine Dosage=mid

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	2.85385	4.98000	4.78800	3.41944	4.80952	4.27288	4.45263	5.43778	4.38448	5.33333	5.56279	5.05000	4.61206	0.233695	12
15	3.75185	6.03478	5.17500	4.27059	5.80667	5.83077	5.90952	6.85000	5.27857	6.60385	6.14444	6.80357	5.70497	0.275663	12
30	4.28929	6.50000	5.60000	4.17727	5.72000	5.77586	6.14615	5.21154	5.47333	6.71000	5.73333	7.10833	5.70376	0.253138	12
45	4.81429	6.33043	4.97667	3.59444	4.47143	5.60333	5.87241	5.74483	5.35862	6.25000	5.22273	7.14000	5.44827	0.270367	12
60	4.66897	6.65333	4.44091	3.92353	5.33333	5.98571	6.57083	6.39286	5.49333	6.22333	3.67500	6.87500	5.51968	0.320690	12
75	4.65926	6.41429	4.44091	4.27647	4.70000	5.96923	5.69583	5.77917	5.65333	6.34000	5.40000	6.76667	5.50793	0.238059	12
90	5.48966	6.53793	4.94483	4.14167	4.23750	5.38400	5.82500	5.02500	5.63333	6.22000	5.17000	6.65000	5.43824	0.231777	12
105	5.14074	6.38400	4.76190	3.90000	4.32222	5.19286	6.34815	5.22500	5.17000	5.79130	5.12500	6.56667	5.32732	0.236869	12
120	5.39667	6.66667	4.72000	4.32857	4.04667	5.20385	5.95000	5.00000	5.11333	5.83913	3.88000	6.51379	5.22156	0.260988	12
135	5.40370	6.66364	4.67273	3.33571	3.91250	4.84118	6.27083	.	4.66667	5.42800	4.27692	6.07778	5.04997	0.310158	11
150	5.27000	6.53846	4.46667	3.72222	3.92500	4.82917	5.88000	.	4.50000	5.54762	5.94667	6.24800	5.17035	0.286047	11
165	4.89565	6.67692	4.32500	3.61429	4.23636	4.67826	5.72727	.	4.20435	5.31000	5.77273	5.98667	5.03886	0.281191	11
180	4.71333	6.71579	4.03214	3.53889	5.00000	4.20000	5.61154	.	5.35000	5.73529	5.55000	5.75600	5.10936	0.278263	11

Response variable=VAGTONE Pyridostigmine Dosage=ctrl

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	1.83590	4.90213	1.45652	1.11579	1.62368	0.04375	2.61538	3.56000	1.82500	2.58333	3.15789	5.65000	2.53078	0.460243	12
15	2.31429	5.33571	1.41154	1.26667	2.80000	0.66190	4.85238	2.81000	3.64800	4.25500	3.04286	5.08333	3.12347	0.448749	12
30	2.01786	5.26667	3.16538	1.47222	3.00000	0.59667	4.45600	2.82174	3.03667	4.54348	2.86000	6.30000	3.29472	0.465820	12
45	2.38333	4.87692	0.75000	1.44118	2.66667	0.63846	4.28000	1.92174	2.73667	4.13750	2.84828	3.10000	2.64840	0.387272	12
60	2.80333	4.80476	1.86071	0.60000	2.34000	0.95000	4.72143	2.90000	2.57000	3.24800	3.30667	3.90000	2.83374	0.377231	12
75	2.92692	4.70000	2.57692	0.25000	1.95000	1.37931	4.94545	2.27917	2.71000	3.10400	3.60667	2.96000	2.78237	0.375041	12
90	3.15263	4.85217	2.08800	0.16364	2.35000	1.07333	4.79600	3.02857	2.55000	2.71579	3.25333	3.29286	2.77636	0.384595	12
105	3.53182	5.12500	2.93571	1.58636	2.85000	1.51379	4.78095	1.81818	2.07333	2.13750	3.09333	3.84615	2.94101	0.346916	12
120	3.56897	4.64444	3.06552	0.00000	2.32500	1.69333	4.74483	1.76364	2.20000	1.67000	2.17333	3.75000	2.63325	0.397044	12
135	3.61739	4.80833	3.12143	.	2.72000	1.69500	4.81250	1.83913	1.96897	1.85000	2.36667	3.54286	2.94021	0.345388	11
150	3.02963	4.25714	2.66923	.	2.58462	2.22500	4.67667	3.05000	1.87333	1.99048	1.97333	3.47647	2.89145	0.281514	11
165	3.60417	4.72308	2.95769	.	2.63200	0.70000	4.81538	0.41667	1.94667	1.75789	2.09333	3.62222	2.66083	0.440316	11
180	3.74211	4.25000	3.03889	.	2.42353	1.00667	4.55882	2.58095	1.53333	1.87143	1.95000	3.27500	2.74825	0.342872	11

Response variable=VAGTONE Pyridostigmine Dosage=high

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	2.87843	3.08750	0.47297	0.92857	1.99444	0.98889	4.77966	3.01190	2.00755	1.75312	3.81897	2.38571	2.34231	0.362224	12
15	2.75556	4.08750	1.65500	2.08500	3.51538	5.05714	5.46190	2.80000	3.07857	4.48214	5.40357	3.85000	3.68598	0.364555	12
30	2.23704	3.49286	0.63750	2.32778	3.10000	4.11250	4.40370	2.79500	3.27333	3.94333	5.07333	5.88333	3.43998	0.402383	12
45	2.31111	3.68571	0.29565	0.86471	2.80741	3.92800	3.82000	2.07200	2.62609	2.95400	3.97241	4.55000	2.82476	0.373053	12
60	1.83704	2.92000	0.82381	1.71250	2.58800	4.25200	3.81786	2.02500	3.71786	3.81333	4.17333	2.23333	2.82617	0.324362	12
75	3.59310	5.20000	0.49231	1.06154	2.88571	4.30714	4.56000	2.06667	2.00333	3.08000	4.66333	3.95000	3.15526	0.432084	12
90	2.93704	4.56667	0.82353	1.53750	2.80909	4.32667	4.74615	2.39091	3.08333	2.81000	4.95172	3.10000	3.17355	0.369804	12
105	4.06333	4.73810	1.42609	2.00000	2.80000	4.29000	5.01667	3.24000	2.41034	3.17407	4.90000	.	3.45987	0.370739	11
120	4.15909	4.67059	1.22273	1.62222	2.74000	4.51250	4.72308	3.05357	2.66000	3.05000	4.08000	3.46364	3.32978	0.333857	12
135	4.08333	4.84000	2.05000	1.95556	2.07500	3.99630	5.21875	3.17500	2.05172	2.95714	4.22667	4.80000	3.45246	0.354019	12
150	4.05926	4.20000	2.00000	1.45625	2.95625	3.36207	5.35000	4.06667	1.46667	3.12000	3.79655	4.20000	3.33614	0.346220	12
165	3.63929	4.08421	2.27857	1.98571	2.80000	2.90000	5.93846	.	3.66897	2.71304	3.70000	3.35000	3.36893	0.322816	11
180	3.54444	4.18889	2.60000	2.46667	2.75000	2.16111	5.92800	.	2.87000	2.62941	3.61724	4.10000	3.35052	0.328736	11

Response variable=VAGTONE Pyridostigmine Dosage=low

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	1.49091	5.01000	2.01471	0.93000	3.65610	1.47885	3.00000	1.71000	1.60893	0.95690	3.67500	3.67500	2.43387	0.380949	12
15	2.70833	4.82000	3.52222	2.07333	3.60000	3.95556	4.10000	1.81364	3.03571	2.95455	4.32857	4.50000	3.45099	0.275202	12
30	1.96429	5.10000	3.76364	3.02500	3.58889	4.13000	4.24500	1.69259	3.09000	3.61667	4.59667	4.54000	3.61273	0.298400	12
45	.	5.10000	2.75000	2.16364	3.14615	4.27600	4.21905	1.06000	2.59000	3.35909	3.28966	4.90000	3.35033	0.365714	11
60	3.96667	5.35000	2.60833	1.70000	2.48125	4.01724	4.17083	0.32500	3.14667	3.38000	2.78333	4.30000	3.18578	0.385528	12
75	.	5.08889	2.88276	1.32500	2.48333	3.60714	4.50870	1.08696	1.16667	3.85294	2.98333	.	2.89857	0.443976	10
90	.	5.05625	2.85217	0.40000	2.67895	2.76552	4.79259	1.44400	0.23667	3.19565	3.04667	.	2.64685	0.508067	10
105	0.46667	4.55000	2.78333	1.98333	2.94167	3.02759	4.92500	0.32917	0.40000	3.04615	3.26154	.	2.51950	0.477063	11
120	.	4.97500	2.61538	1.65000	2.65714	2.65926	4.60000	0.00000	2.98519	3.09286	3.27692	3.00000	2.86470	0.399419	11
135	.	4.23000	2.20833	1.31429	3.20000	2.44000	4.57727	2.12667	1.06667	2.89259	3.09667	.	2.71525	0.357976	10
150	1.60000	5.03846	2.94286	0.76667	3.06500	2.24286	4.87273	1.46316	1.68889	3.25909	3.35333	.	2.75391	0.413386	11
165	.	4.45455	2.80417	0.91667	3.23529	1.89600	4.81053	1.30000	3.12400	2.74167	3.37692	3.47778	2.92160	0.360824	11
180	3.50000	4.02500	2.58750	0.00000	2.84545	1.73462	4.87857	1.07407	2.36500	2.78846	3.63750	1.85000	2.60718	0.385920	12

Response variable=VAGTONE Pyridostigmine Dosage=mid

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	0.48974	3.54333	1.07200	1.18611	2.80238	0.89153	2.44737	2.55556	2.56897	3.99365	3.16977	3.81111	2.37763	0.346009	12
15	1.25185	4.48261	1.74286	1.72353	4.44000	4.08846	4.93333	5.08750	3.85000	5.46154	4.37407	5.04643	3.87352	0.422107	12
30	1.41429	5.20476	1.42727	2.76364	3.17500	4.25862	5.08846	3.10769	3.52000	4.99000	3.79000	5.46667	3.68387	0.400944	12
45	2.33929	5.09130	1.47000	2.35556	2.98571	3.53333	3.69655	3.49655	3.28276	4.16538	2.40455	5.72000	3.37842	0.348757	12
60	2.30345	5.64667	0.94545	2.15882	3.22000	3.78571	5.30000	3.52857	3.74333	4.62333	0.31250	4.83750	3.36711	0.483230	12
75	2.64444	5.40000	1.39545	2.16471	2.74545	3.55385	3.99167	3.39583	3.81000	4.66000	1.60909	4.88333	3.35449	0.369845	12
90	3.49655	5.00690	1.57931	0.94167	2.81250	2.87600	4.83125	3.00000	3.68000	4.37667	1.61000	4.57308	3.23199	0.389753	12
105	3.27407	5.16800	1.82857	1.31250	2.58889	2.96071	5.05926	3.08750	2.80333	4.23478	2.27500	4.42222	3.25124	0.356416	12
120	3.46000	5.50476	2.23600	0.40000	2.57333	2.55769	4.95385	3.25000	1.68000	4.22609	1.82000	4.39655	3.08819	0.431540	12
135	3.43333	5.47727	1.78182	1.96429	2.62500	2.71765	4.83750	.	1.13333	3.44000	1.15385	4.53333	3.00885	0.446345	11
150	3.26333	5.43077	2.20741	0.44444	2.70000	2.40833	4.53200	.	0.71667	3.57619	2.25333	4.44400	2.90695	0.467266	11
165	2.65217	5.43846	1.85500	0.78571	2.96364	2.24783	4.61818	.	1.02609	4.02000	2.46818	4.44000	2.95593	0.454658	11
180	2.82333	4.98947	1.22857	1.22222	2.93750	3.10000	4.34615	.	3.26667	3.98824	2.61364	4.21600	3.15744	0.363277	11

APPENDIX H

ANOVAS FOR P-Q INTERVALS FOLLOWING PYRIDOSTIGMINE BROMIDE
(EXPERIMENT II), USING ALL ANIMALS,
FOR THE FOUR EXPERIMENTAL WEEKS

NUMBER OF OBSERVATIONS IN DATA SET = 768

General Linear Models Procedures SAS

Dependent Variable: P-Q Interval

Experiment #: II (Pyridostigmine bromide)

Source	DF	Sum of Squares	F-Value	PR > F
Model	383	0.095	5.79	0.0001
Error	378	0.016		
Corrected Total	761	0.111		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	0.058	168.91	0.0001
Animal*Dose (Group)	24	0.007	6.60	0.0001
Dose*Time	42	0.002	1.14	0.2560
Animal*Time(Group)	112	0.005	1.13	0.2020

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	0.006	0.28	0.8383

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	0.001	1.40	0.2670
Group*Dose	6	0.002	1.13	0.3759
Week	3	0.0003	0.36	0.7826

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	14	0.003	4.03	0.0001
Group*Time	42	0.002	1.01	0.4731

APPENDIX I

ANOVAS FOR PLASMA AND ERYTHROCYTE CHOLINESTERASE FOLLOWING PYRIDOSTIGMINE BROMIDE (EXPERIMENT II), USING ALL ANIMALS, FOR THE FOUR EXPERIMENTAL WEEKS

NUMBER OF OBSERVATIONS IN DATA SET = 144

General Linear Models Procedures SAS

Dependent Variable: Plasma Cholinesterase

Source	DF	Sum of Squares	F-Value	PR > F
Model	75	166.45	16.32	0.0001
Error	68	9.36		
Corrected Total	143	177.81		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	77.12	71.84	0.0001
Animal*Dose (Group)	24	3.63	1.20	0.2773
Animal*Time (Group)	16	3.90	1.77	0.0543
Dose*Time	6	-	19.41	0.0001

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	9.32	0.31	0.8149

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	24.33	49.08	0.0001
Group*Dose	6	1.43	1.44	0.2431
Week	3	.87	1.76	0.1846

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	2	17.08	35.07	0.0001

APPENDIX J

MEAN PLASMA AND ERYTHROCYTE CHOLINESTERASE ACTIVITY
(EXPERIMENT II)

Plasma Cholinesterase Activity (mM/l/min) for Monkeys Receiving

Four Pyridostigmine Bromide Treatment Conditions

Animal #	Time (min)	Pyridostigmine Dosage (μg/kg) 0	100	200	400
C02	-30	3.765	4.358	3.052	3.549
	30	3.478	2.321	1.508	1.118
	180	3.826	2.737	1.984	1.878
C04	-30	3.475	2.979	4.135	4.007
	30	4.228	3.514	2.470	1.647
	180	4.538	3.506	3.017	2.161
C06	-30	0.969	0.867	1.500	1.234
	30	1.162	1.020	0.836	0.726
	180	1.269	0.823	0.828	0.646
N538	-30	1.735	2.501	3.158	2.773
	30	2.958	1.687	2.072	1.744
	180	2.959	2.369	2.237	1.871
N584	-30	2.583	2.087	1.971	1.765
	30	2.426	1.800	1.214	0.838
	180	2.694	2.040	1.387	1.231
N597	-30	1.663	1.519	1.891	2.008
	30	1.741	1.194	1.026	0.878
	180	2.079	1.355	1.151	1.099
OLX	-30	2.525	2.474	2.597	3.085
	30	2.571	2.259	1.419	1.209
	180	2.582	2.196	1.576	1.255
OL3	-30	2.720	2.315	2.524	2.382
	30	2.621	1.821	1.523	0.997
	180	2.783	1.917	1.631	1.160
OPE324	-30	3.834	4.382	4.130	4.239
	30	3.966	3.353	2.388	1.590
	180	4.069	2.543	2.046	1.896

Animal #	Time (min)	Pyridostigmine Dosage (µg/kg) 0	100	200	400
OPE352	-30	2.964	2.644	2.667	2.717
	30	3.106	2.224	1.700	0.925
	180	3.104	2.033	1.765	1.337
OPW	-30	4.018	5.507	4.785	5.603
	30	5.647	3.580	2.991	2.209
	180	5.048	4.300	3.109	2.356
005	-30	3.895	3.723	3.201	3.849
	30	3.358	2.566	2.401	1.425
	180	3.314	2.679	2.084	1.458

Grand Means (n = 12)

Time (min)	Pyridostigmine Dosage (µg/kg) 0	100	200	400
-30	3.107	2.769	2.968	3.101
(SEM)	(0.271)	(0.341)	(0.287)	(0.352)
30	3.213	2.379	1.796	1.276
(SEM)	(0.375)	(0.252)	(0.191)	(0.130)
180	3.278	2.484	1.901	1.529
(SEM)	(0.303)	(0.269)	(0.196)	(0.145)

Erythrocyte Cholinesterase Activity (mM/l/min) for Monkeys Receiving Four Pyridostigmine Bromide Treatment Conditions

Animal #	Time (min)	Pyridostigmine Dosage (µg/kg) 0	100	200	400
C02	-30	3.082	3.223	2.473	3.248
	30	2.824	1.075	0.921	0.576
	180	3.033	2.177	2.026	2.013
C04	-30	3.292	2.631	3.292	3.148
	30	3.476	2.000	1.128	0.735
	180	3.524	3.506	3.640	2.621
C06	-30	2.055	2.185	2.492	2.121
	30	2.012	1.391	1.425	0.619
	180	3.034	1.421	1.623	1.023
N538	-30	3.370	2.123	3.459	3.545
	30	3.282	2.000	1.831	1.433
	180	2.962	3.344	3.462	3.023
N584	-30	3.102	2.423	2.332	2.219
	30	3.087	1.792	0.830	0.953
	180	3.193	2.360	1.933	1.331
N597	-30	3.430	2.825	3.554	3.516
	30	2.550	1.568	1.129	1.104
	180	3.126	2.768	2.691	2.510
OLX	-30	2.839	2.944	2.729	2.719
	30	2.319	2.001	1.517	1.072
	180	3.221	2.530	1.884	1.887
OL3	-30	2.094	1.603	1.872	2.341
	30	2.248	0.498	0.466	0.436
	180	2.473	1.649	1.439	1.242
OPE324	-30	2.292	2.376	2.417	2.383
	30	2.036	2.027	0.851	0.672
	180	3.275	2.351	2.052	1.677
OPE352	-30	3.823	3.232	3.166	3.667
	30	4.011	1.466	1.293	1.029
	180	4.134	2.786	3.065	1.930
OPW	-30	3.425	3.715	3.204	3.393
	30	3.594	1.830	1.373	0.796
	180	3.959	2.590	2.344	2.176

Animal #	Time (min)	Pyridostigmine Dosage (μg/kg) 0	100	200	400
005	-30	2.339	2.291	1.669	2.079
	30	2.152	0.853	0.575	0.822
	180	2.441	1.748	2.039	1.107

Grand Means (n = 12)

Time (min)	Pyridostigmine Dosage (µg/kg) 0	100	200	400
-30	2.936	2.686	2.722	2.865
(SEM)	(0.197)	(0.155)	(0.178)	(0.177)
30	2.758	1.818	1.112	0.854
(SEM)	(0.229)	(0.203)	(0.116)	(0.080)
180	3.206	2.583	2.350	1.878
(SEM)	(0.190)	(0.168)	(0.205)	(0.183)

APPENDIX K

ANOVAS FOR VAGAL TONE MONITORING VARIABLES
FOLLOWING PYRIDOSTIGMINE BROMIDE AND ATROPINE SULFATE
(EXPERIMENT III), USING ALL ANIMALS,
FOR THE FOUR EXPERIMENTAL WEEKS

NUMBER OF OBSERVATIONS IN DATA SET = 562

General Linear Models Procedures SAS

Dependent Variable: Heart Rate

Source	DF	Sum of Squares	F-Value	PR > F
Model	311	363457.16	9.50	0.0001
Error	250	30764.82		
Corrected Total	561	394221.98		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	42188.70	42.85	0.0001
Animal*Dose (Group)	24	23979.76	8.12	0.0001
Dose*Time	33	19690.19	4.85	0.0001
Animal*Time (Group)	88	16096.66	1.49	0.0090

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	155610.21	9.84	0.0046

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	30240.19	10.09	0.0002
Group*Dose	6	3402.90	0.57	0.7519
Week	3	4732.38	1.58	0.2212

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	11	33918.63	16.86	0.0001
Group*Time	33	4916.30	0.81	0.7430

Dependent Variable: Heart Period

Source	DF	Sum of Squares	F-Value	PR > F
Model	311	4011287.06	5.61	0.0001
Error	250	574798.21		
Corrected Total	561	4586085.27		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	345311.16	18.77	0.0001
Animal*Dose (Group)	24	341563.19	6.19	0.0001
Dose*Time	33	232777.10	3.07	0.0001
Animal*Time (Group)	88	208002.35	1.03	0.4260

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	1593587.46	12.31	0.0023

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	269116.46	6.30	0.0026
Group*Dose	6	90995.33	1.07	0.4100
Week	3	24938.04	0.58	0.6312

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	11	421862.22	16.23	0.0001
Group*Time	33	118902.23	1.52	0.0617

Dependent Variable: Heart Period Variance

Source	DF	Sum of Squares	F-Value	PR > F
Model	311	943.24	12.63	0.0001
Error	250	60.02		
Corrected Total	561	1003.26		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	60.60	31.55	0.0001
Animal*Dose (Group)	24	42.57	7.39	0.0001
Dose*Time	33	90.13	11.38	0.0001
Animal*Time (Group)	88	40.46	1.92	0.0001

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	184.27	8.11	0.0083

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	304.64	57.24	0.0001
Group*Dose	6	20.78	1.95	0.1130
Week	3	28.04	5.27	0.0062

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	11	109.05	21.56	0.0001
Group*Time	33	12.71	0.84	0.7116

Dependent Variable: Vagal Tone

Source	DF	Sum of Squares	F-Value	PR > F
Model	311	1802.86	14.06	0.0001
Error	250	103.06		
Corrected Total	561	1905.92		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	187.28	56.79	0.0001
Animal*Dose (Group)	24	129.72	13.11	0.0001
Dose*Time	33	130.66	9.60	0.0001
Animal*Time (Group)	88	46.68	1.29	0.0670

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	374.12	5.33	0.0261

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	457.08	28.19	0.0001
Group*Dose	6	50.99	1.57	0.1984
Week	3	24.12	1.49	0.2431

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	11	261.05	44.74	0.0001
Group*Time	33	26.79	1.53	0.0599

APPENDIX L

FIFTEEN-MINUTE MEANS OF VAGAL TONE VARIABLES
FOLLOWING PYRIDOSTIGMINE BROMIDE
BY ATROPINE SULFATE TREATMENT AND BY ANIMAL
(EXPERIMENT III)

Response variable=HR Atropine Dosage=ctrl

TIME	OLX	OPE352	_005	C02	C06	N538	N597	N584	OPE324	OL3	OPW	C04	_MEAN	_S_E	_N
0	96.000	137.509	132.583	178.000	146.778	156.727	173.273	133.236	172.712	136.377	115.696	.	143.536	7.6611	11
15	48.500	114.963	117.810	165.583	143.700	169.176	157.923	121.857	159.643	136.800	105.750	140.250	131.830	9.7038	12
30	83.647	106.533	117.333	158.696	144.077	163.111	151.357	115.000	157.739	129.818	101.586	139.500	130.700	7.4468	12
45	122.000	114.583	126.917	162.842	154.560	159.111	154.000	120.800	142.667	144.333	111.310	145.385	138.209	5.2544	12
60	101.538	109.733	128.105	155.360	136.733	151.750	144.267	121.385	142.733	140.250	100.947	136.400	130.767	5.3717	12
75	97.667	118.533	131.789	154.414	138.345	158.095	151.517	127.154	147.267	150.500	95.931	135.333	133.879	6.0511	12
90	102.957	126.370	128.235	161.786	137.043	185.231	153.733	135.091	135.067	139.615	104.400	140.500	137.502	6.5456	12
105	113.833	132.000	140.267	160.759	139.786	167.440	156.621	150.667	145.733	141.379	98.552	158.200	142.103	5.7430	12
120	101.059	126.000	140.444	157.778	141.360	179.412	157.636	139.680	131.846	138.276	100.250	155.400	139.095	6.6125	12
135	107.680	126.875	141.524	158.273	142.545	195.091	160.267	136.963	136.200	136.133	102.067	168.353	142.664	7.3863	12
150	114.846	127.048	145.600	159.923	144.435	193.000	158.000	134.348	137.133	144.560	96.621	162.077	143.133	7.1211	12
165	97.789	129.077	137.172	163.789	138.190	177.600	161.630	137.182	143.800	145.760	107.241	163.474	141.892	6.7401	12
180	48.750	127.733	156.417	166.000	139.840	199.000	167.400	137.692	146.600	135.143	109.379	167.905	141.822	10.8024	12
195	122.000	129.200	146.143	167.000	156.000	181.333	188.500	132.533	161.000	152.143	152.000	165.500	154.446	5.8116	12

Response variable=HR Atropine Dosage=high

TIME	OLX	OPE352	_005	C02	C06	N538	N597	N584	OPE324	OL3	OPW	C04	_MEAN	_S_E	_N
0	137.491	125.429	124.333	180.596	160.964	170.150	168.679	134.696	203.435	167.000	134.509	173.407	156.724	7.20588	12
15	110.593	113.071	116.444	172.714	140.857	167.200	134.400	125.500	163.000	141.333	115.760	146.545	137.285	6.31854	12
30	99.120	96.690	120.000	170.783	146.933	162.444	134.800	114.200	145.241	130.500	103.867	137.889	130.206	6.97162	12
45	102.889	105.667	141.583	187.429	174.560	164.615	160.483	147.500	148.800	159.182	122.069	143.833	146.551	7.46240	12
60	145.000	128.857	177.538	196.000	171.000	201.048	189.043	204.333	176.316	175.826	126.200	197.500	174.055	7.83743	12
75	138.519	132.222	158.421	186.667	163.103	193.889	177.067	181.700	171.565	169.214	151.111	183.500	167.248	5.56395	12
90	140.364	128.929	148.857	184.125	156.621	212.833	176.667	178.214	176.231	162.690	149.931	184.667	166.677	6.69406	12
105	134.222	130.897	159.538	177.083	157.310	211.111	181.217	165.846	164.240	159.133	146.429	176.889	163.660	6.29750	12
120	134.609	126.833	153.478	173.000	160.148	208.333	177.647	171.280	164.240	156.000	149.862	181.333	163.064	6.28267	12
135	133.280	128.222	151.417	175.778	154.444	198.667	173.500	166.556	167.273	159.600	153.067	173.500	161.275	5.54695	12
150	138.348	128.690	147.000	173.600	153.400	200.444	166.714	162.000	157.200	162.154	150.828	169.909	159.191	5.30755	12
165	138.571	128.000	180.083	171.714	158.960	208.182	165.647	172.000	160.087	155.517	144.733	174.143	163.137	6.06614	12
180	146.615	129.533	150.857	168.286	160.000	191.909	179.333	165.789	156.261	152.600	150.067	104.154	154.617	6.52709	12
195	147.200	116.667	138.000	167.143	169.000	183.000	.	150.667	154.667	172.800	183.000	.	158.214	6.63588	10

Response variable=HR Atropine Dosage=low

TIME	OLX	OPE352	_005	C02	C06	N538	N597	N584	OPE324	OL3	OPW	C04	_MEAN	_S_E	_N
0	115.102	159.063	154.364	183.862	154.649	157.333	165.123	147.951	159.920	169.826	136.912	166.240	155.862	4.9910	12
15	109.600	122.286	128.211	171.478	133.333	175.067	136.815	166.500	134.556	163.625	132.720	141.250	142.953	6.0878	12
30	82.235	122.333	125.833	164.786	131.533	151.800	134.783	165.833	131.800	139.310	118.286	114.889	131.952	6.6069	12
45	101.867	117.636	130.190	171.417	147.704	173.200	147.263	170.364	128.074	146.769	120.069	67.071	135.135	9.0427	12
60	98.909	109.455	16.519	165.214	128.867	138.421	126.800	180.444	118.667	151.310	110.069	117.412	130.174	7.0580	12
75	80.000	119.059	122.091	159.120	142.667	192.444	139.200	158.000	142.828	168.000	119.172	146.000	140.715	8.2859	12
90	93.231	123.467	142.000	167.586	135.000	186.571	153.034	166.429	158.741	152.357	127.857	166.471	147.729	7.2422	12
105	114.429	123.000	161.273	175.500	133.333	189.800	163.333	164.267	142.800	155.684	130.071	159.091	151.048	6.4933	12
120	116.727	126.069	140.074	169.158	138.000	196.750	161.103	151.294	143.133	165.586	135.862	159.647	150.284	6.2655	12
135	115.652	122.552	135.133	164.429	138.160	181.143	173.933	158.400	130.621	166.400	133.103	170.714	149.187	6.4356	12
150	126.857	120.667	70.267	169.739	135.652	203.600	157.429	.	146.000	151.185	134.345	172.300	144.367	10.3079	11
165	107.250	119.852	71.448	163.727	134.200	192.000	163.400	.	148.370	156.500	126.667	181.882	142.300	10.5495	11
180	121.733	128.414	127.000	162.476	135.143	176.000	167.360	.	153.889	154.074	128.733	181.400	148.747	6.4670	11
195	.	123.857	148.667	165.750	154.571	192.000	172.000	.	154.909	155.500	139.600	155.882	156.274	5.7790	10

Response variable=HR Atropine Dosage=med

TIME	OLX	OPE352	_005	C02	C06	N538	N597	N584	OPE324	OL3	OPW	C04	_MEAN	_S_E	_N
0	137.843	123.214	118.500	177.125	161.872	155.143	177.280	156.667	175.309	124.978	144.423	180.667	152.752	6.56937	12
15	104.462	108.800	104.880	166.400	157.565	153.077	148.357	130.167	133.000	128.444	131.545	139.385	133.840	5.91092	12
30	97.778	94.444	114.800	163.333	142.235	157.895	130.414	128.345	123.333	59.667	113.333	152.600	123.181	8.61517	12
45	100.273	101.333	116.909	150.455	172.769	159.125	155.034	170.320	138.786	.	121.111	178.333	142.223	8.56746	11
60	109.100	114.667	119.852	163.714	169.800	175.231	182.074	194.333	159.000	177.333	140.552	204.583	159.187	9.09756	12
75	118.348	120.880	134.519	170.250	189.391	178.714	198.786	163.364	171.222	.	150.857	203.846	163.652	8.91099	11
90	126.522	120.067	150.750	167.000	185.267	179.444	199.630	170.400	155.600	159.000	148.296	194.593	163.047	7.17093	12
105	133.714	124.333	151.565	165.500	179.333	178.600	186.667	170.069	160.600	.	145.000	187.920	162.118	6.43301	11
120	137.714	130.800	167.300	160.300	.	177.067	182.069	166.667	171.267	150.600	166.348	186.000	163.285	5.25560	11
135	129.565	134.933	152.933	156.880	.	173.467	172.929	163.478	162.733	145.333	145.000	177.826	155.916	4.82115	11
150	124.286	126.000	156.174	163.444	.	176.471	177.538	156.200	162.583	.	133.556	175.636	155.189	6.47245	10
165	122.941	120.800	148.846	159.826	.	173.750	165.286	163.053	164.207	.	154.640	173.474	154.682	5.96838	10
180	122.320	121.034	152.250	164.583	.	161.455	183.778	164.667	157.933	.	142.714	169.000	153.973	6.35025	10
195	118.000	133.867	149.692	147.800	.	158.857	.	156.571	170.000	156.000	146.750	174.000	151.154	5.18556	10

Response variable=HPER Atropine Dosage=ctrl

TIME	OLX	OPE352	_005	C02	C06	N538	N597	N584	OPE324	OL3	OPW	C04	_MEAN	_S_E	_N
0	584.538	439.088	453.438	336.972	409.056	384.886	346.709	450.218	347.390	441.226	521.000	.	428.593	23.0016	11
15	824.667	524.963	511.857	362.292	417.850	356.353	380.192	493.857	378.286	445.133	569.208	428.250	474.409	37.6199	12
30	719.706	564.167	516.074	378.652	419.115	369.667	397.714	521.577	382.435	466.455	591.414	429.750	479.727	30.7895	12
45	494.333	534.583	475.000	368.737	390.960	379.278	390.500	498.840	423.296	420.778	544.483	414.000	444.566	17.8795	12
60	592.577	547.400	470.211	386.200	438.833	396.563	415.800	494.385	422.233	431.125	596.737	439.550	469.301	21.0899	12
75	615.792	507.833	456.684	389.379	434.793	382.286	396.793	471.731	408.733	401.875	625.379	442.333	461.134	23.9979	12
90	584.304	475.370	468.529	371.500	437.913	325.308	390.167	444.545	446.067	430.077	580.267	427.250	448.441	21.7355	12
105	527.667	454.200	427.667	374.069	429.786	359.960	383.552	398.000	413.667	427.310	609.276	379.200	432.029	20.6505	12
120	594.882	476.000	440.222	381.259	425.400	335.059	380.318	430.240	457.346	436.276	599.625	385.650	445.190	23.3620	12
135	557.880	473.313	426.000	380.455	420.727	308.909	374.567	438.148	444.200	441.900	592.600	356.353	434.588	23.1172	12
150	523.077	473.286	412.700	376.462	415.870	313.500	380.300	447.565	438.633	418.440	622.138	370.385	432.696	23.1669	12
165	596.278	465.692	438.655	367.316	434.571	341.667	371.000	438.591	417.833	414.880	560.483	367.684	434.554	22.2489	12
180	860.500	470.900	389.083	362.158	429.960	302.429	360.350	437.038	412.033	447.857	550.379	357.238	448.327	41.8195	12
195	486.000	464.400	412.357	358.500	386.333	331.000	318.000	452.600	373.000	399.000	395.600	362.250	394.920	15.0055	12

Response variable=HPER Atropine Dosage=high

TIME	OLX	OPE352	_005	C02	C06	N538	N597	N584	OPE324	OL3	OPW	C04	_MEAN	_S_E	_N
0	439.655	478.619	483.528	332.745	373.732	353.500	357.500	446.174	296.674	361.500	447.964	348.593	393.349	17.9678	12
15	543.889	532.107	516.333	348.000	426.929	361.000	447.560	481.200	368.182	427.286	522.880	411.364	448.894	20.1872	12
30	605.680	621.241	503.885	351.391	411.200	370.222	445.150	526.150	413.448	460.429	578.267	434.444	476.792	26.0251	12
45	587.111	575.944	430.292	320.571	344.480	365.846	382.207	409.250	407.720	379.182	502.690	418.250	426.962	24.6940	12
60	416.500	465.476	342.769	306.273	351.179	299.048	317.087	293.500	339.684	341.391	481.333	304.250	354.874	18.6335	12
75	433.185	453.556	379.000	320.933	369.207	309.722	338.467	331.050	349.217	354.643	396.815	326.583	363.532	13.0203	12
90	427.864	465.857	403.238	325.438	383.897	282.500	339.619	336.786	340.385	368.690	399.931	324.556	366.563	14.8735	12
105	447.185	458.759	376.077	338.792	383.483	284.556	331.087	361.769	365.200	377.000	409.500	338.889	372.691	14.1486	12
120	445.826	473.167	390.913	346.750	375.370	288.833	338.471	351.920	366.000	384.679	400.414	330.500	374.404	14.5104	12
135	450.160	467.778	396.292	341.611	389.741	302.533	345.250	360.722	358.955	376.733	392.000	345.688	377.289	13.4075	12
150	435.739	466.517	408.000	345.750	391.267	300.000	359.429	371.400	382.633	371.423	397.483	353.318	381.913	12.5007	12
165	447.952	470.483	356.917	349.786	378.920	288.727	362.235	349.316	375.696	385.655	414.767	343.571	377.002	14.1201	12
180	410.269	465.067	398.071	356.714	375.880	312.591	334.444	362.789	384.478	394.150	400.233	628.000	401.891	23.4096	12
195	407.200	513.333	433.500	359.571	356.500	327.400	.	397.833	388.000	349.400	329.000	.	386.174	17.8433	10

Response variable=HPER Atropine Dosage=low

TIME	OLX	OPE352	_005	C02	C06	N538	N597	N584	OPE324	OL3	OPW	C04	_MEAN	_S_E	_N
0	522.204	377.875	389.568	325.897	388.541	382.333	363.807	405.634	383.280	353.435	438.158	361.560	391.024	14.3610	12
15	554.800	493.321	470.211	349.783	451.167	343.533	439.519	360.000	445.667	368.188	452.240	445.375	431.150	18.5319	12
30	688.400	493.792	478.667	363.750	462.133	397.400	447.826	361.917	455.400	433.414	507.143	583.833	472.806	26.5333	12
45	595.000	512.909	494.714	352.667	412.741	351.300	413.947	352.636	476.444	418.308	504.517	825.591	475.898	38.5397	12
60	615.364	549.636	517.926	363.964	465.767	434.842	473.640	332.278	508.300	396.724	546.414	530.188	477.920	24.1198	12
75	750.893	507.647	491.682	378.120	435.133	311.556	432.100	399.167	419.759	361.000	504.448	424.000	451.292	32.0407	12
90	645.846	489.667	426.000	358.793	445.350	323.000	392.690	361.071	378.926	394.321	469.857	360.235	420.480	24.9717	12
105	530.571	491.100	388.773	341.650	450.333	317.200	367.333	365.933	421.933	386.579	461.643	377.045	408.341	18.3915	12
120	514.727	478.448	429.037	354.684	435.158	307.125	372.655	412.882	419.900	363.414	442.966	376.000	408.916	16.5583	12
135	521.000	490.793	446.533	365.929	435.000	332.000	345.600	380.600	459.586	361.267	451.793	352.786	411.907	18.1860	12
150	475.905	500.167	756.500	354.174	443.913	295.200	382.000	.	411.556	397.704	447.655	349.100	437.625	36.6372	11
165	560.500	502.444	880.034	368.182	448.200	314.000	367.167	.	405.000	385.333	475.067	330.353	457.844	47.9032	11
180	495.400	468.276	474.423	370.762	445.524	341.600	363.600	.	390.667	394.370	466.733	332.400	413.069	17.6397	11
195	.	489.000	405.333	363.750	388.571	312.000	350.000	.	387.364	388.583	433.600	385.765	390.397	15.0324	10

Response variable=HPER Atropine Dosage=med

TIME	OLX	OPE352	_005	C02	C06	N538	N597	N584	OPE324	OL3	OPW	C04	_MEAN	_S_E	_N
0	436.137	489.036	506.893	339.688	371.362	387.321	340.220	385.407	344.855	482.49	416.346	330.333	402.507	18.2481	12
15	577.846	552.867	573.000	360.500	380.913	392.538	405.714	461.917	452.346	467.94	457.864	457.923	461.781	21.1471	12
30	615.000	634.889	534.240	366.958	422.412	380.789	460.931	472.276	486.833	1047.25	529.458	392.600	528.636	53.3028	12
45	599.227	596.667	526.455	399.636	347.231	379.125	391.207	358.480	437.714	.	502.519	338.611	443.352	29.2962	11
60	560.350	525.444	541.519	366.714	352.900	344.923	329.074	308.444	379.300	339.00	427.966	292.917	397.379	27.1869	12
75	509.826	496.280	447.000	353.500	317.522	335.571	302.393	395.864	352.167	.	398.571	294.000	382.063	22.6009	11
90	474.391	500.400	402.583	359.667	324.933	335.667	301.444	352.733	385.867	377.13	404.667	308.148	377.302	17.8309	12
105	453.286	484.033	394.500	363.000	334.333	336.200	321.133	353.138	374.000	.	413.893	319.040	376.960	16.4269	11
120	436.619	460.967	366.100	375.000	.	339.933	329.034	359.333	352.067	399.10	364.913	322.421	373.226	13.0707	11
135	463.913	447.133	394.000	382.920	.	346.667	346.821	367.522	368.500	411.00	417.857	337.565	389.445	12.6009	11
150	482.893	478.148	371.654	368.111	.	341.176	338.115	384.900	368.625	.	452.074	341.455	392.715	17.9226	10
165	488.059	497.800	402.889	375.522	.	346.813	362.643	369.737	366.276	.	391.800	346.053	394.759	17.2907	10
180	491.280	498.655	397.792	365.292	.	371.818	327.000	365.333	380.033	.	422.607	354.650	397.446	18.1048	10
195	507.625	449.200	402.846	407.500	.	377.857	.	383.143	352.000	384.00	410.375	344.000	401.855	15.1334	10

Response variable=HPERVAR Atropine Dosage=ctrl

TIME	OLX	OPE352	_005	C02	C06	N538	N597	N584	OPE324	OL3	OPW	C04	_MEAN	_S_E	_N
0	7.01875	4.20877	5.99792	4.23333	4.57778	3.56136	3.70182	4.82909	3.62542	5.53208	5.76304	.	4.82267	0.339201	11
15	9.61250	6.14815	6.50952	4.96667	4.57000	3.93529	5.18077	6.53929	4.53929	5.42667	6.76667	5.65000	5.82040	0.430424	12
30	7.96471	6.40667	6.65185	5.31304	5.09231	4.16111	5.27143	6.46154	4.52174	4.91364	6.64828	5.90000	5.77553	0.314577	12
45	6.26667	6.46250	6.32083	5.02632	4.59600	4.53333	4.98000	6.48000	5.45926	5.43333	6.58966	6.18462	5.69438	0.223667	12
60	6.48462	6.00667	6.34737	5.64400	5.11333	4.57500	4.67333	6.16923	5.54000	4.58750	6.53684	6.13000	5.65066	0.215589	12
75	6.96250	5.91667	3.80000	5.58621	5.59655	4.20952	5.30000	6.08846	5.33000	5.14583	6.72069	6.06667	5.56026	0.263899	12
90	6.79565	6.13704	4.70000	5.28214	5.16957	4.31538	5.38000	5.69091	5.79000	4.99615	6.65333	6.05000	5.58001	0.217234	12
105	6.21250	5.58000	4.51333	5.53103	5.21429	3.98000	4.74138	5.14167	5.69667	5.24828	6.85862	5.71500	5.36940	0.219743	12
120	6.50000	5.40000	5.73333	5.48519	5.50400	4.21176	4.55455	5.11600	6.00385	5.17931	6.89583	5.76500	5.52907	0.215510	12
135	6.27600	5.71250	6.32381	5.43636	5.21364	4.20909	4.82000	5.31481	5.65667	5.30333	6.93667	5.80000	5.58357	0.207959	12
150	5.57308	5.30476	5.41000	5.42692	5.31304	3.99167	4.51333	5.47826	5.99000	4.91200	7.15517	5.99231	5.42171	0.227556	12
165	6.30000	5.58462	5.95517	5.22632	5.47143	4.00000	4.99259	5.30455	5.28000	5.68000	6.68966	5.86842	5.52940	0.196507	12
180	9.24375	5.70333	6.50417	5.28947	5.18400	4.13571	4.41500	5.16923	5.41000	4.97143	6.22414	5.84762	5.67482	0.378628	12
195	6.80000	5.68000	5.92143	5.22500	5.46667	4.30000	4.67500	4.88000	4.26667	5.52143	5.62000	5.92500	5.35677	0.212349	12

Response variable=HPERVAR Atropine Dosage=high

TIME	OLX	OPE352	_005	C02	C06	N538	N597	N584	OPE324	OL3	OPW	C04	_MEAN	_S_E	_N
0	4.63273	4.54286	6.52500	4.26809	4.45179	3.48250	4.00893	4.58913	1.66304	5.42500	5.05818	4.08148	4.39406	0.333900	12
15	5.95926	5.81071	7.20556	5.10000	4.95000	4.06000	5.38000	6.04000	4.09091	5.15238	5.89600	5.76364	5.45070	0.251692	12
30	6.15200	6.44138	6.89615	5.08261	5.47333	4.21667	5.56000	6.35500	5.20000	5.13571	6.29000	5.83889	5.72015	0.216675	12
45	5.62222	6.09444	6.67083	3.06429	3.80400	4.80000	4.01379	5.58750	4.91600	4.51818	6.07241	6.10833	5.10600	0.318551	12
60	4.38333	3.66190	3.97692	2.34545	3.55714	3.30476	2.34348	2.80000	2.01579	2.73478	4.94667	2.40000	3.20585	0.265274	12
75	3.79630	4.02593	2.91053	3.21333	3.34483	2.32222	2.25333	2.25500	2.60870	3.26071	2.80370	2.68333	2.95649	0.168957	12
90	4.26818	3.60357	2.34762	3.01250	4.19310	2.98333	2.27619	2.31786	2.55769	3.50000	3.26207	2.78889	3.09258	0.199760	12
105	3.69259	4.10690	3.17692	3.32917	4.31034	2.18889	2.07391	1.93846	2.75200	3.27333	3.35357	2.30000	3.04134	0.229206	12
120	3.97391	4.15000	3.13478	3.89286	3.95556	1.96667	2.86471	2.76000	2.82800	3.43929	3.43103	2.38333	3.23168	0.200145	12
135	3.92400	4.21481	3.58333	3.53333	4.00741	2.10667	2.55833	2.83889	3.29091	3.78333	3.64333	2.70625	3.34922	0.189161	12
150	3.98696	4.41379	4.10000	3.60000	4.47667	1.96667	2.62857	2.59600	3.41000	3.33846	3.58276	2.94091	3.42007	0.223618	12
165	5.13810	3.82414	4.42917	3.78929	4.00800	2.45455	2.78824	2.61579	3.23913	3.43793	3.41000	2.01429	3.42905	0.255276	12
180	4.20769	4.88667	3.95000	4.20476	4.[illegible]200	1.81364	2.23333	2.88947	3.39565	3.58000	3.53667	3.84615	3.55300	0.252249	12
195	5.16000	4.46667	4.95000	4.77143	.[illegible]000	2.66000	.	3.20000	3.30000	4.50000	4.15000	.	4.14081	0.260839	10

Response variable=HPERVAR Atropine Dosage=low

TIME	OLX	OPE352	_005	C02	C06	N538	N597	N584	OPE324	OL3	OPW	C04	_MEAN	_S_E	_N
0	6.07551	3.38125	4.54545	3.98966	4.87838	3.33333	4.17719	5.07073	4.22400	4.23478	4.69649	5.25600	4.48857	0.225053	12
15	7.00000	5.46429	5.53684	5.05217	5.18333	3.12667	5.52222	4.68750	4.98333	4.78125	5.29600	6.46250	5.25801	0.273801	12
30	7.80588	6.18750	6.88750	5.19643	5.67000	4.22500	6.02609	4.51667	5.54000	4.54138	5.59286	6.16667	5.69633	0.296653	12
45	7.20000	6.29091	7.59524	5.33750	5.48148	5.32000	5.74211	4.60909	6.07037	5.62692	6.10690	7.51429	6.07457	0.269998	12
60	7.29545	6.65455	7.05926	5.77500	5.84667	5.17895	6.61600	4.53889	5.40667	3.94828	6.75517	6.84118	5.99300	0.305630	12
75	7.98214	6.03529	6.72273	6.09200	5.42667	4.37778	5.91000	4.91667	4.75862	3.96800	6.18621	5.58889	5.66375	0.315267	12
90	7.83846	6.27333	6.55517	5.41379	5.45000	3.25714	5.18966	4.58571	5.38148	4.68571	5.78214	5.86471	5.52311	0.326085	12
105	6.95000	6.24333	6.14091	5.08500	6.00000	3.80000	4.93333	4.70667	5.64333	4.67895	5.45714	5.86364	5.45853	0.248276	12
120	7.03636	6.50000	6.05556	5.11579	5.56316	3.80000	4.72069	5.75294	5.54667	4.04138	5.25862	6.04118	5.45270	0.272975	12
135	6.93913	6.81379	6.48333	5.24643	5.94800	3.87143	5.20333	5.82000	5.76552	4.46667	5.71034	5.72857	5.66638	0.257822	12
150	5.87619	6.74000	8.75333	5.45652	5.79565	3.52000	5.05714	.	5.16296	4.63333	5.57931	5.03500	5.60086	0.398228	11
165	6.28333	7.03704	7.96897	5.37727	5.94500	2.10000	5.43333	.	5.18889	4.32917	5.74667	4.47059	5.44366	0.461250	11
180	7.00667	6.75517	6.66923	5.65714	5.91429	4.02000	4.85600	.	5.36111	4.45185	5.91667	4.42000	5.54801	0.308171	11
195	.	6.87143	5.91111	5.67500	5.34286	3.60000	5.20000	.	4.89091	5.08333	5.46000	5.75882	5.37935	0.264003	10

Response variable=HPERVAR Atropine Dosage=med

TIME	OLX	OPE352	_005	C02	C06	N538	N597	N584	OPE324	OL3	OPW	C04	_MEAN	_S_E	_N
0	4.52549	4.67679	6.44464	4.11875	4.21277	3.79286	3.42000	4.47778	2.95636	5.38444	4.51538	4.93333	4.45488	0.261652	12
15	6.43846	6.96667	7.33200	4.77000	4.69130	4.15385	5.24643	5.72917	4.88846	5.40556	5.34091	6.43077	5.61613	0.283599	12
30	6.61852	6.71111	7.04400	5.26667	4.89412	4.46842	5.97931	6.06897	5.48000	6.50000	5.29583	5.84000	5.84725	0.227831	12
45	6.03636	6.50476	7.16818	5.63636	3.15385	5.16875	5.47931	4.40000	5.77857	.	6.08519	4.47222	5.44396	0.335276	11
60	6.27500	5.26667	6.64444	4.55714	3.22000	3.68462	3.20000	3.63333	3.18000	2.93333	4.18966	3.17917	4.16361	0.366851	12
75	5.06087	4.66400	6.03704	4.15000	2.47826	3.05714	3.07857	4.73636	3.40556	.	3.67500	3.41923	3.97837	0.318026	11
90	4.64783	5.28333	6.03750	3.96667	2.90333	3.03333	2.96667	3.99333	4.04667	3.12500	3.81481	3.77407	3.96605	0.278842	12
105	5.57857	5.43333	6.10000	4.68750	2.60000	3.17000	3.82667	4.41034	3.66333	.	3.80000	3.78000	4.27725	0.325192	11
120	4.38095	5.48667	5.45500	4.87500	.	3.19333	3.86207	4.40000	2.83667	3.07000	3.38261	4.04737	4.08997	0.279290	11
135	4.86522	5.39333	5.53667	5.05200	.	2.91333	4.61071	4.16087	3.29333	2.86667	3.46786	4.66087	4.25644	0.294156	11
150	4.96071	5.52593	6.22308	4.57222	.	2.95294	3.83462	4.11000	2.97917	.	4.24074	4.73636	4.41358	0.326404	10
165	5.57059	5.40000	5.48519	4.97826	.	3.80000	3.94286	4.11579	3.01724	.	3.93200	4.92632	4.51682	0.274947	10
180	6.00000	5.74828	5.35833	4.92083	.	3.64091	3.14444	4.04667	3.63333	.	3.72857	4.87500	4.50964	0.316035	10
195	6.03750	5.50000	5.67692	5.48000	.	4.04286	.	4.02857	4.70000	3.50000	3.42500	5.30000	4.76909	0.302806	10

Response variable=VAGTONE Atropine Dosage=ctrl

TIME	OLX	OPE352	_005	C02	C06	N538	N597	N584	OPE324	OL3	OPW	C04	_MEAN	_S_E	_N
0	5.67500	1.74035	3.59375	2.35833	1.76667	1.65455	0.22727	1.70364	0.73390	1.54717	4.48696	.	2.31705	0.491130	11
15	8.65000	5.02222	4.55238	3.40833	1.93000	1.75882	2.21923	5.07143	2.34643	1.37333	5.71250	3.58750	3.80268	0.610630	12
30	7.02353	5.29667	4.59259	3.06087	1.35000	2.46667	2.54286	2.92308	1.81304	1.88636	6.05172	3.57500	3.54853	0.521561	12
45	4.91667	4.74167	4.23750	3.02632	1.85600	2.60000	1.58333	3.82400	3.15926	2.18333	4.96552	3.92308	3.41806	0.344922	12
60	4.90769	4.80333	3.97368	3.50800	1.10667	1.92500	1.98667	1.79231	2.86333	1.27500	5.55789	4.15500	3.15455	0.443024	12
75	5.87500	4.09667	1.27895	3.91379	1.46897	2.31429	1.74483	1.26923	2.90333	1.27083	6.18276	4.51667	3.06961	0.522393	12
90	5.69565	4.01111	1.91176	3.80000	1.60000	1.63846	1.73333	1.50455	3.51333	1.09615	5.68333	4.10000	3.02397	0.477202	12
105	4.67500	4.00000	2.04000	3.82759	1.61071	2.28800	1.64138	1.71667	3.23333	0.98621	6.32069	3.86000	3.01663	0.454065	12
120	5.34706	4.40000	3.71667	3.92593	1.64400	2.19412	1.45909	2.05600	3.88846	1.26897	6.05417	3.73000	3.30704	0.453177	12
135	5.02000	4.10625	4.20000	3.70455	1.73182	1.19091	1.09667	2.30370	3.34000	1.06000	6.27333	3.78824	3.15129	0.485937	12
150	4.21538	4.28095	2.67667	3.79615	2.05652	1.49167	1.25333	3.11304	3.31667	1.26800	6.75517	3.93462	3.17985	0.458687	12
165	5.22632	3.80385	3.75172	3.57895	1.74762	1.28667	1.20000	2.54545	2.57000	1.09600	5.44483	3.82105	3.00604	0.434449	12
180	8.26250	3.89000	4.27083	3.55789	1.71600	0.91429	1.08500	3.02692	2.61667	1.33810	5.20690	3.63333	3.29320	0.598153	12
195	5.10000	3.82000	3.65000	3.47500	2.00000	1.86667	0.62500	1.37333	1.68333	1.32857	4.14000	4.02500	2.75724	0.412604	12

Response variable=VAGTONE Atropine Dosage=high

TIME	OLX	OPE352	_005	C02	C06	N538	N597	N584	OPE324	OL3	OPW	C04	_MEAN	_S_E	_N
0	2.61455	2.79524	4.91389	2.60851	2.08750	1.30500	0.94464	1.86957	0.00000	2.85000	2.43455	2.15556	2.21492	0.346780	12
15	4.47778	4.33929	5.90556	2.82143	2.03571	2.36667	3.49200	3.90500	1.31364	1.16667	4.35200	3.78182	3.32980	0.409939	12
30	4.30400	5.45862	5.38077	2.35217	2.10667	2.58333	3.47000	4.02000	3.06552	1.55000	5.13333	4.23889	3.63861	0.383019	12
45	3.33333	4.37222	4.17917	0.87143	0.75600	2.33077	1.38966	3.17500	2.54800	0.95909	4.17586	4.04167	2.67768	0.404644	12
60	0.41667	0.13333	1.60769	0.00000	0.12857	0.00000	0.42609	0.00000	0.00000	0.00000	2.53000	0.35000	0.46603	0.228489	12
75	0.25556	0.07778	1.21053	0.00000	0.02414	0.00000	0.00000	0.00000	0.00000	0.11071	0.13333	0.66667	0.20656	0.106593	12
90	0.32273	0.33929	0.62857	0.26875	0.08621	0.00000	0.00000	0.09286	0.00000	0.10345	0.43103	1.45556	0.31070	0.118684	12
105	0.37407	0.32414	1.20000	0.00000	0.16552	0.00000	0.18696	0.00000	0.00000	0.08333	0.46071	0.23333	0.25234	0.097580	12
120	0.73043	0.47500	1.53913	0.12857	0.24074	0.00000	0.30588	0.00000	0.00000	0.15357	0.20690	0.23333	0.33446	0.125365	12
135	0.57600	0.23704	1.82917	0.14444	0.06667	0.00000	0.13333	0.08889	0.00000	0.14333	0.34667	0.11250	0.30650	0.145926	12
150	0.55652	0.33793	1.76667	0.00000	0.07000	0.00000	0.00000	0.11200	0.04667	0.23462	0.48276	0.10455	0.30931	0.143432	12
165	1.45238	0.33448	2.53333	0.00000	0.35200	0.00000	0.34706	0.00000	0.00000	0.11379	0.72667	0.07857	0.49486	0.221769	12
180	1.02692	0.70000	2.44286	0.18571	0.58800	0.00000	0.00000	0.00000	0.00000	0.00000	0.56667	0.36923	0.48995	0.203552	12
195	1.06000	1.46667	3.30000	0.00000	0.00000	0.00000	.	0.00000	0.00000	0.00000	0.00000	.	0.58267	0.345924	10

Response variable=VAGTONE Atropine Dosage=low

TIME	OLX	OPE352	_005	C02	C06	N538	N597	N584	OPE324	OL3	OPW	C04	_MEAN	_S_E	_N
0	4.70000	0.55312	2.51591	1.87586	2.53243	0.86667	0.82632	1.80732	2.09800	0.53043	2.78596	3.14000	2.01934	0.356006	12
15	5.58000	4.03571	3.53158	3.06087	2.05833	1.00000	3.64074	2.77500	3.81667	1.13125	3.03200	4.15000	3.15101	0.375099	12
30	6.88235	4.08333	4.77500	2.95000	1.45000	1.93500	3.68261	1.25833	4.05000	0.63448	3.91429	4.41667	3.37601	0.512138	12
45	5.70000	4.39091	5.74286	2.97083	3.05185	2.92000	3.16842	0.53636	3.90000	1.03077	4.31724	5.38929	3.59321	0.482768	12
60	5.81364	3.61818	4.52222	4.15000	1.07667	3.72632	4.28800	0.45000	2.41667	0.36207	4.80000	4.30000	3.29365	0.518745	12
75	7.14286	2.84118	3.93182	4.31600	0.95333	0.58889	2.78667	1.75000	0.96897	0.30000	3.84138	2.98889	2.70083	0.567077	12
90	6.68077	3.94000	3.96897	3.19655	0.72000	0.68571	1.43793	1.32857	1.78519	0.06429	3.53571	3.57059	2.57619	0.548749	12
105	4.99286	3.87667	3.02727	2.43500	1.40000	0.62000	0.93667	1.84667	3.43000	0.41579	3.55000	3.52727	2.50485	0.420798	12
120	5.78182	3.89310	3.52593	2.92105	2.23684	0.40000	1.38966	1.69412	2.90333	0.06207	3.25172	3.80000	2.65497	0.463644	12
135	5.35217	4.47241	4.21000	3.41071	2.09200	0.95714	1.54000	3.04000	3.90690	0.12000	3.25517	3.60000	2.99638	0.443866	12
150	3.71905	4.97667	6.51000	3.18261	2.53478	0.00000	2.60000	.	2.49259	0.05185	3.33793	3.13500	2.95823	0.565817	11
165	5.35000	4.97407	5.56207	3.65455	2.49500	0.00000	2.24333	.	2.50000	0.07500	3.85000	2.34118	3.00411	0.573678	11
180	5.12667	4.50690	4.43462	3.74762	2.49048	1.40000	2.15600	.	2.51667	0.30741	3.74333	1.66000	2.91724	0.454262	11
195	.	4.81429	4.40000	3.90000	2.87143	0.00000	2.60000	.	2.20909	0.50833	3.46000	3.45294	2.82161	0.496327	10

Response variable=VAGTONE Atropine Dosage=med

TIME	OLX	OPE352	_005	C02	C06	N538	N597	N584	OPE324	OL3	OPW	C04	_MEAN	_S_E	_N
0	2.30588	2.44286	4.45536	1.72500	1.03404	1.32857	0.41000	1.65556	0.96545	1.40889	1.74231	2.83333	1.85894	0.306081	12
15	4.86923	5.57333	5.45600	2.82000	1.46087	1.60000	2.35357	3.36667	3.40385	0.76667	3.08182	4.33846	3.25754	0.454062	12
30	5.11852	5.53333	4.80400	2.61667	1.24118	2.12105	3.11034	3.63103	3.38000	2.86667	3.65417	3.68500	3.48016	0.357562	12
45	4.32727	5.16667	5.27727	3.03636	0.38462	2.80000	2.08966	1.22400	3.20000	.	4.05185	1.53333	3.00828	0.484330	11
60	4.64500	1.47778	3.33333	0.30714	0.00000	0.31538	0.00000	0.22778	0.27333	0.23333	1.51379	0.24167	1.04738	0.430220	12
75	1.55652	0.79200	1.98148	0.32500	0.00000	0.00000	0.00000	0.54091	0.00000	.	0.41071	0.05385	0.51459	0.205233	11
90	2.51739	1.29333	1.97083	0.11667	0.00000	0.00000	0.00000	0.00000	0.12000	0.13750	0.46667	0.35556	0.58150	0.249661	12
105	2.84286	1.73000	1.88333	0.08750	0.96667	0.00000	0.00000	0.16207	0.07000	.	0.45357	0.28000	0.77055	0.291515	11
120	2.11905	1.70333	2.45500	0.19500	.	0.00000	0.02414	0.95000	0.04667	0.21000	0.16087	0.60000	0.76946	0.274346	11
135	2.97826	2.00667	1.54667	0.68000	.	0.00000	0.00000	0.69565	0.02333	0.46667	0.08929	1.30435	0.89008	0.293075	11
150	3.02143	2.31481	2.40769	0.54444	.	0.00000	0.13846	2.01000	0.24583	.	0.62963	1 45000	1.27623	0.348198	10
165	3.71176	2.50000	1.92593	1.33913	.	0.00000	0.05000	1.75263	0.17931	.	0.12800	1.95789	1.35447	0.396372	10
180	4.32000	3.28276	1.54167	1.26250	.	0.03182	0.00000	1.52000	0.28333	.	0.15000	2.08500	1.44771	0.462029	10
195	4.50000	2.50667	2.08462	2.94000	.	0.25714	.	1.42143	0.00000	0.00000	0.11250	2.80000	1.66224	0.492517	10

APPENDIX M

ANOVAS FOR P-Q INTERVALS FOLLOWING PYRIDOSTIGMINE BROMIDE AND ATROPINE SULFATE (EXPERIMENT III), USING ALL ANIMALS, FOR THE FOUR EXPERIMENTAL WEEKS

NUMBER OF OBSERVATIONS IN DATA SET = 960

General Linear Models Procedures SAS

Dependent Variable: P-Q Intervals

Source	DF	Sum of Squares	F-Value	PR > F
Model	465	0.08	2.20	0.0001
Error	376	0.02		
Corrected Total	841	0.09		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	0.02	53.55	0.0001
Animal*Dose (Group)	24	0.01	6.16	0.0001
Dose*Time	54	0.00	1.01	0.4630
Animal*Time (Group)	143	0.01	1.12	0.1920

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	0.02	2.54	0.1295

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	0.01	7.52	0.0010
Group*Dose	6	0.00	0.94	0.4838
Week	3	0.00	4.64	0.0108

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	18	0.01	7.34	0.0001
Group*Time	53	0.00	1.24	0.1560

APPENDIX N

ANOVAS FOR PLASMA AND ERYTHROCYTE CHOLINESTERASE
FOLLOWING PYRIDOSTIGMINE BROMIDE AND ATROPINE SULFATE
(EXPERIMENT III), USING ALL ANIMALS,
FOR THE FOUR EXPERIMENTAL WEEKS

NUMBER OF OBSERVATIONS IN DATA SET = 143

General Linear Models Procedures SAS

All animals received 200 µg pyridostigmine bromide per kg body weight at time 0.

Dose refers to atropine sulfate doses.

Dependent Variable: Plasma Cholinesterase

Source	DF	Sum of Squares	F-Value	PR > F
Model	77	104.87	36.29	0.0001
Error	65	3.28		
Corrected Total	142	144.15		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	66.04	163.75	0.0001
Animal*Dose (Group)	24	0.79	0.65	0.8782
Animal*Time (Group)	16	5.32	6.59	0.0001
Dose*Time	6	-	0.70	0.6470

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	25.06	1.01	0.4364

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	1.61	16.36	0.0001
Group*Dose	6	1.62	8.25	0.0001
Week	3	2.43	24.72	0.0001

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	2	37.70	56.69	0.0001

Dependent Variable: Erythrocyte Cholinesterase

Source	DF	Sum of Squares	F-Value	PR > F
Model	77	104.44	24.63	0.0001
Error	65	3.58		
Corrected Total	142	108.02		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	19.86	45.07	0.0001
Animal*Dose (Group)	24	1.23	0.93	0.5601
Animal*Time (Group)	16	2.45	2.78	0.0019
Dose*Time	6	-	0.70	0.6500

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	2.01	0.27	0.8456

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	0.15	0.96	0.4257
Group*Dose	6	0.63	2.03	0.1002
Week	3	0.67	4.35	0.0139

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	2	73.31	239.73	0.0001

APPENDIX O

MEAN PLASMA AND ERYTHROCYTE CHOLINESTERASE ACTIVITY
(EXPERIMENT III)

Plasma Cholinesterase Activity (mM/l/min) for Monkeys Receiving

200 µg/kg Pyridostigmine Bromide and Four Atropine Sulfate

Treatment Conditions

Animal #	Time (min)	Pyridostigmine Dosage (µg/kg) 0	100	200	400
C02	-30	3.045	3.784	3.630	3.337
	30	2.093	1.945	2.200	1.559
	180	2.562	2.330	2.200	2.304
C04	-30	4.000	4.462	4.104	4.240
	30	2.703	2.429	2.308	2.180
	180	3.014	2.803	2.543	2.839
C06	-30	1.184	1.122	1.372	1.088
	30	0.898	0.843	1.000	0.798
	180	0.940	1.087	1.099	0.932
N538	-30	3.452	3.976	3.848	3.462
	30	2.652	2.727	2.743	2.218
	180	2.403	2.893	2.664	2.031
N584	-30	2.528	2.674	2.221	2.432
	30	1.502	1.584	1.178	1.169
	180	1.310	1.493	1.543	1.483
N597	-30	1.972	2.129	2.564	1.466
	30	1.446	1.492	1.856	1.255
	180	1.409	1.697	1.819	1.405
OLX	-30	2.863	2.593	3.092	3.079
	30	1.630	1.430	1.787	1.878
	180	1.692	-	2.207	1.968
OL3	-30	2.585	2.423	3.650	3.107
	30	1.826	1.610	2.258	2.493
	180	1.840	1.651	2.197	1.691
OPE324	-30	3.876	4.042	3.932	3.906
	30	2.703	3.409	2.583	3.306
	180	2.450	2.496	2.538	2.219

Animal #	Time (min)	Pyridostigmine Dosage (μg/kg) 0	100	200	400
OPE352	-30	2.470	2.254	2.776	2.481
	30	1.546	1.682	2.420	1.886
	180	1.369	1.786	1.738	1.861
OPW	-30	4.774	4.878	6.252	5.618
	30	4.031	3.593	4.063	4.145
	180	3.370	2.801	3.418	3.400
005	-30	3.747	2.675	3.551	3.463
	30	2.174	2.123	2.919	2.546
	180	2.051	2.024	2.226	2.149

Grand Means (n = 12)

Time (min)	Pyridostigmine Dosage (µg/kg) 0	100	200	400
-30	3.041	3.084	3.416	3.140
(SEM)	(0.285)	(0.323)	(0.347)	(0.350)
30	2.100	2.131	2.276	2.199
(SEM)	(0.240)	(0.254)	(0.233)	(0.271)
180	2.034	2.041	2.184	2.024
(SEM)	(0.214)	(0.176)	(0.173)	(0.189)

Erythrocyte Cholinesterase Activity (mM/l/min) for Monkeys Receiving 200 µg/kg Pyridostigmine Bromide and Four Atropine Sulfate Treatment Conditions

Animal #	Time (min)	Pyridostigmine Dosage (µg/kg) 0	100	200	400
C02	-30	2.188	3.324	3.046	3.254
	30	1.114	1.226	1.103	1.340
	180	2.603	2.451	2.280	2.244
C04	-30	4.127	4.253	3.876	4.065
	30	1.987	1.779	1.703	1.946
	180	3.518	3.407	2.969	3.137
C06	-30	2.932	2.558	3.003	2.580
	30	1.333	1.331	1.154	1.217
	180	2.576	2.423	2.322	2.136
N538	-30	3.786	3.500	3.251	3.354
	30	1.438	1.498	1.765	1.077
	180	2.896	3.017	3.081	2.967
N584	-30	3.335	3.531	3.122	3.186
	30	1.638	1.117	1.079	1.278
	180	3.188	2.551	3.156	2.756
N597	-30	3.269	2.792	3.368	2.978
	30	1.715	1.484	1.457	1.280
	180	2.824	2.803	2.905	2.821
OLX	-30	3.516	3.405	3.231	3.158
	30	1.435	2.633	1.713	1.676
	180	2.419	-	2.749	2.796
OL3	-30	2.404	2.204	3.068	2.659
	30	0.746	1.023	1.217	1.418
	180	1.825	2.033	2.100	2.147
OPE324	-30	3.006	2.978	3.091	2.205
	30	1.523	1.456	1.527	1.781
	180	2.597	2.704	2.458	2.373
OPE352	-30	3.673	3.612	3.749	2.660
	30	1.519	1.469	1.889	1.417
	180	2.712	3.108	2.955	3.139
OPW	-30	3.684	3.767	4.351	4.402
	30	2.177	1.890	1.761	2.265
	180	3.285	3.499	3.625	3.865

Animal #	Time (min)	Pyridostigmine Dosage (µg/kg) 0	100	200	400
005	-30	2.664	2.168	2.557	2.542
	30	1.152	0.883	1.254	1.045
	180	2.122	2.080	1.254	2.281

Grand Means (n = 12)

Time (min)	Atropine Dosage (µg/kg) 0	14	44	140
-30	3.215	3.174	3.309	3.087
(SEM)	(0.170)	(0.185)	(0.137)	(0.184)
30	1.481	1.378	1.469	1.479
(SEM)	(0.111)	(0.092)	(0.085)	(0.106)
180	2.713	2.726	2.734	2.722
(SEM)	(0.138)	(0.135)	(0.134)	(0.149)

APPENDIX P

ANOVAS FOR VAGAL TONE MONITORING VARIABLES
FOLLOWING PHYSOSTIGMINE SALICYLATE (EXPERIMENT IV),
USING ALL ANIMALS, FOR THE FOUR EXPERIMENTAL WEEKS

NUMBER OF OBSERVATIONS IN DATA SET = 565

General Linear Models Procedures SAS

Dependent Variable: Heart Rate

Source	DF	Sum of Squares	F-Value	PR > F
Model	311	337685.34	8.16	0.0001
Error	253	33666.39		
Corrected Total	564	371351.73		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	119534.88	112.29	0.0001
Animal*Dose (Group)	24	49460.70	15.49	0.0001
Dose*Time	33	5480.65	1.25	0.174
Animal*Time (Group)	88	30455.27	2.60	0.0001

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	63716.82	1.42	0.3063

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	8503.15	1.38	0.2742
Group*Dose	6	5773.30	0.47	0.8259
Week	3	9673.41	1.56	0.2238

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	11	6681.46	1.76	0.0744
Group*Time	33	10748.92	0.94	0.5652

Dependent Variable: Heart Period

Source	DF	Sum of Squares	F-Value	PR > F
Model	311	4265119.43	6.51	0.0001
Error	253	530576.64		
Corrected Total	564	4795696.07		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	1488563.96	88.38	0.0001
Animal*Dose (Group)	24	632564.18	12.52	0.0001
Dose*Time	33	70756.07	1.02	0.4450
Animal*Time (Group)	88	342927.35	1.85	0.0001

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	724691.38	1.30	0.3400

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	127358.69	1.61	0.2131
Group*Dose	6	65587.53	0.41	0.8619
Week	3	94784.07	1.20	0.3314

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	11	74672.64	1.74	0.0771
Group*Time	33	185844.43	1.45	0.0890

Dependent Variable: Heart Period Variance

Source	DF	Sum of Squares	F-Value	PR > F
Model	311	569.28	6.63	0.0001
Error	253	73.20		
Corrected Total	564	642.48		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	202.27	87.38	0.0001
Animal*Dose (Group)	24	89.71	12.92	0.0001
Dose*Time	33	26.21	2.74	0.0001
Animal*Time (Group)	88	64.99	2.55	0.0001

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	78.03	1.03	0.4300

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	19.92	1.78	0.1784
Group*Dose	6	8.56	0.38	0.8833
Week	3	7.14	0.64	0.5985

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	11	22.23	2.74	0.0043
Group*Time	33	17.74	0.73	0.8472

Dependent Variable: Vagal Tone

Source	DF	Sum of Squares	F-Value	PR > F
Model	311	1549.07	12.33	0.0001
Error	253	102.19		
Corrected Total	564	1651.26		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	766.86	237.33	0.0001
Animal*Dose (Group)	24	185.25	19.11	0.0001
Dose*Time	33	53.38	4.00	0.0001
Animal*Time (Group)	88	96.33	2.71	0.0001

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	246.16	0.86	0.5018

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	36.61	1.58	0.2199
Group*Dose	6	22.36	0.48	0.8145
Week	3	6.05	0.26	0.8523

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	11	31.24	2.59	0.0066
Group*Time	33	25.42	0.70	0.8716

FIFTEEN-MINUTE MEANS OF VAGAL TONE VARIABLES
BY PHYSOSTIGMINE SALICYLATE TREATMENT AND BY ANIMAL
(EXPERIMENT IV)

Response variable=HR Physostigmine Dosage=ctrl

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	164.792	181.444	172.912	150.632	131.000	155.760	96.690	141.135	154.655	114.143	137.796	122.038	143.583	7.17306	12
15	144.667	146.133	154.250	164.154	166.588	149.200	115.000	143.769	170.375	112.222	136.462	117.250	143.339	5.75193	12
30	146.000	147.333	181.733	160.286	170.200	155.333	114.000	142.476	140.600	111.333	138.667	130.148	144.843	5.97458	12
45	168.000	196.667	171.267	174.750	161.529	173.857	.	176.857	164.733	129.077	153.926	147.556	165.293	5.30329	11
60	149.133	152.000	140.133	169.000	143.200	155.667	120.000	134.783	156.200	117.259	153.733	121.778	142.741	4.73658	12
75	146.533	152.889	131.933	184.600	149.167	151.647	115.667	141.037	167.800	120.963	133.793	120.273	143.025	5.85754	12
90	141.310	163.000	123.867	181.500	145.043	149.700	74.571	148.741	176.733	126.345	135.000	123.517	140.777	8.17206	12
105	140.615	162.000	122.069	186.600	141.077	146.000	.	146.571	181.800	126.133	155.286	130.556	148.973	6.34926	11
120	134.609	162.444	109.600	186.833	137.800	145.133	116.333	151.091	181.172	126.519	125.067	139.400	143.000	6.93963	12
135	133.133	171.667	111.917	172.778	142.762	145.273	116.000	146.560	164.200	124.667	135.133	162.316	143.867	5.98637	12
150	148.133	164.500	108.733	166.667	140.000	155.857	116.000	146.667	175.867	117.545	132.533	157.619	144.177	6.26103	12
165	139.800	160.857	122.714	172.364	137.273	168.476	107.333	158.933	179.724	144.533	137.600	137.667	147.273	6.15470	12
180	137.067	160.800	127.467	175.250	146.143	162.762	.	151.481	169.533	149.800	140.714	128.000	149.911	4.82502	11

Response variable=HR Physostigmine Dosage=high

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	168.682	167.481	175.760	156.560	119.630	162.296	109.250	127.333	125.451	122.073	142.897	126.078	141.958	6.65050	12
15	161.667	158.000	197.520	190.000	178.476	165.857	100.000	162.643	134.000	139.000	161.556	134.917	156.970	7.75358	12
30	141.000	178.500	194.222	177.913	117.481	156.923	124.400	127.067	175.538	172.000	157.000	111.467	152.793	8.02039	12
45	158.000	165.043	175.200	162.500	125.524	171.467	123.200	115.067	171.538	162.100	173.071	146.643	154.113	6.17361	12
60	151.333	160.000	164.533	141.133	123.667	194.250	126.000	100.267	161.133	155.133	165.778	148.833	149.338	7.01075	12
75	150.000	160.074	163.200	135.172	128.786	185.600	120.727	89.067	166.800	150.800	152.600	149.133	145.997	7.21993	12
90	144.000	171.500	153.852	136.348	124.462	180.000	124.308	94.077	171.667	148.069	143.158	146.267	144.809	6.88087	12
105	161.636	169.524	155.517	147.846	128.552	182.667	125.600	96.267	184.733	146.667	136.154	136.867	147.669	7.32263	12
120	151.091	166.545	154.067	141.263	125.643	184.467	126.000	96.933	176.483	141.333	143.304	138.467	145.466	6.88034	12
135	138.000	165.238	151.379	149.111	124.414	187.133	118.750	99.862	180.643	152.471	136.444	145.200	145.720	7.19581	12
150	128.545	169.789	145.852	161.000	124.138	182.867	113.375	98.600	184.533	143.733	134.600	146.133	144.431	7.70392	12
165	142.000	168.667	139.250	146.333	126.593	176.400	109.000	99.733	187.333	144.733	126.600	151.000	143.137	7.48681	12
180	128.923	173.429	142.966	148.154	129.846	181.259	109.000	101.867	191.448	140.667	130.621	160.067	144.854	7.97312	12

Response variable=HR Physostigmine Dosage=low

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	162.561	170.200	157.750	171.355	108.912	170.517	68.000	141.034	149.286	111.238	126.576	101.020	136.538	9.6418	12
15	153.071	151.143	158.357	174.800	146.087	166.720	107.182	146.706	138.643	109.040	113.143	101.360	138.854	7.2169	12
30	141.333	141.200	170.783	169.000	126.467	172.200	105.250	142.000	139.733	135.310	132.800	104.370	140.037	6.4940	12
45	168.370	143.000	162.154	171.667	123.000	120.148	106.250	133.500	169.533	138.000	139.929	116.963	141.043	6.4934	12
60	157.267	147.750	140.889	135.200	112.720	80.923	107.556	141.280	153.333	126.769	124.200	99.733	127.302	6.7192	12
75	142.533	144.545	141.533	166.800	117.600	167.929	103.700	145.400	172.333	125.867	123.429	112.231	138.658	6.5399	12
90	138.600	144.857	138.552	175.091	119.000	164.933	95.333	128.200	181.267	129.867	120.000	98.000	136.142	7.9043	12
105	136.500	142.000	138.929	186.800	117.600	162.160	64.667	126.667	193.250	125.793	117.103	119.889	135.946	9.8559	12
120	129.071	139.059	133.034	200.500	119.143	157.071	76.000	134.897	146.815	126.000	113.000	125.714	133.359	8.4045	12
135	127.000	145.067	133.034	200.000	119.600	171.273	102.000	134.345	170.533	123.133	107.786	126.783	138.379	8.3080	12
150	136.222	150.143	132.333	209.000	121.862	168.600	70.000	136.133	175.176	121.800	116.286	124.500	138.505	10.0541	12
165	146.133	148.889	125.429	194.714	127.538	168.400	93.333	145.643	.	121.600	111.241	125.760	137.153	8.4063	11
180	134.000	148.625	151.143	193.500	134.087	167.400	70.091	141.615	.	133.000	112.000	118.167	136.693	9.5164	11

Response variable=HR Physostigmine Dosage=mid

TIME	C02	C04	C06	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	168.435	164.783	178.436	166.485	127.417	158.691	118.810	140.279	131.164	118.982	110.857	124.267	142.384	6.8017	12
15	165.067	167.294	170.444	193.667	167.200	164.286	97.429	.	146.750	130.714	173.111	121.000	154.269	8.3512	11
30	143.692	165.600	176.690	193.750	143.214	141.200	100.333	126.000	159.067	172.815	148.133	119.571	149.172	7.5877	12
45	155.077	154.444	172.800	192.909	128.357	152.154	102.455	121.091	153.467	169.043	158.741	108.400	147.411	7.8224	12
60	160.750	145.913	150.966	188.800	113.034	146.333	88.087	120.750	144.200	178.364	144.333	123.793	142.110	8.0328	12
75	160.235	138.133	160.000	190.000	114.800	142.696	81.407	122.769	155.692	169.200	143.310	126.167	142.034	8.2282	12
90	158.533	142.833	161.800	174.000	119.172	154.769	50.769	57.000	167.200	202.000	139.793	133.933	138.484	12.9331	12
105	151.100	146.500	144.552	168.143	114.483	147.750	98.100	118.000	169.733	190.000	139.133	131.185	143.223	7.4197	12
120	152.769	151.120	133.680	168.000	119.357	154.143	94.667	40.444	169.379	174.000	134.500	132.400	135.372	10.8549	12
135	145.684	154.286	150.080	158.625	116.138	149.462	94.235	127.143	166.867	170.000	140.069	140.552	142.762	6.2366	12
150	137.238	152.000	164.500	175.333	120.786	148.364	99.565	121.125	168.933	.	133.448	131.630	141.175	6.9842	11
165	144.071	.	161.308	.	121.667	145.379	91.143	120.667	178.071	161.185	133.862	127.565	138.492	7.9332	10
180	144.750	.	155.214	.	124.400	146.200	109.143	136.400	192.462	154.867	126.867	134.727	142.503	7.1584	10

Response variable=HPER Physostigmine Dosage=ctrl

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	365.377	331.000	347.719	400.132	483.045	385.760	638.276	425.811	388.418	526.643	435.857	492.288	435.027	25.2992	12
15	416.407	410.800	390.167	366.692	361.529	402.160	519.250	419.769	358.563	536.000	440.115	512.125	427.798	18.0087	12
30	412.000	406.667	331.433	375.643	353.700	389.741	526.500	425.429	427.500	540.200	433.000	480.926	425.228	18.4213	12
45	360.167	333.000	353.500	347.125	372.235	351.000	.	345.429	366.033	469.654	395.111	435.778	375.367	12.7272	11
60	403.333	393.500	429.300	355.750	420.533	385.333	501.667	445.435	384.100	512.852	392.133	493.926	426.489	14.9138	12
75	411.067	391.778	454.867	327.100	403.500	396.118	518.667	428.000	358.667	498.111	449.966	503.591	428.452	17.0239	12
90	425.793	369.000	484.733	331.625	414.739	402.100	880.143	405.889	340.433	479.310	445.300	488.379	455.620	41.4557	12
105	429.538	370.200	491.897	321.600	426.808	411.375	.	411.750	330.767	476.300	390.000	473.500	412.158	17.0106	11
120	447.565	368.667	547.433	322.417	436.250	413.233	517.000	398.727	332.759	476.000	482.233	437.650	431.661	19.9674	12
135	455.033	348.833	535.625	349.889	422.476	413.773	514.500	411.880	366.833	481.633	445.267	370.789	426.378	18.0099	12
150	407.833	364.875	552.533	362.133	429.652	385.500	523.000	410.593	341.200	543.682	454.633	403.619	431.604	20.8603	12
165	433.267	376.857	492.571	352.273	438.455	359.810	558.667	381.833	333.931	416.133	442.467	443.208	419.123	18.4630	12
180	440.333	374.200	474.867	342.750	413.643	370.238	.	396.815	354.767	400.800	428.286	474.500	406.473	13.5490	11

Response variable=HPER Physostigmine Dosage=high

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	355.682	362.222	343.160	386.040	501.648	370.426	550.406	473.907	478.549	491.473	425.603	477.765	434.740	20.0125	12
15	370.333	379.375	306.400	315.000	343.667	366.286	600.706	375.607	451.800	442.250	381.944	450.708	398.673	22.9993	12
30	425.950	335.542	310.111	338.957	512.963	385.538	488.150	474.467	345.308	349.000	383.533	545.600	407.927	22.9011	12
45	379.842	364.043	342.733	370.500	481.095	358.733	487.400	528.333	350.808	370.150	347.143	411.429	399.351	18.3540	12
60	396.000	374.679	364.400	425.267	485.250	308.500	478.000	600.633	373.100	386.600	361.667	403.583	413.140	22.1657	12
75	399.000	375.074	368.033	444.448	467.357	323.267	497.318	677.933	359.967	397.767	393.433	402.067	425.472	26.7751	12
90	417.800	349.792	389.778	440.217	483.154	333.300	482.154	644.115	350.000	405.069	419.105	411.933	427.201	24.0610	12
105	372.818	355.095	385.793	407.923	468.034	328.367	477.867	624.000	325.000	409.143	442.077	438.767	419.574	23.5815	12
120	400.955	361.227	389.233	425.421	477.607	324.933	478.000	619.533	341.724	425.000	421.130	434.033	424.900	22.4265	12
135	438.526	363.571	397.310	402.000	482.862	320.433	505.938	602.655	332.643	395.059	442.333	413.500	424.736	22.6141	12
150	468.909	353.526	413.704	375.000	483.207	328.100	529.188	610.700	325.467	417.600	450.633	411.133	430.597	24.3423	12
165	425.182	356.667	431.917	410.167	475.185	340.000	550.200	603.333	320.700	414.533	475.633	397.867	433.449	23.9302	12
180	468.038	346.429	420.862	404.846	462.962	331.296	549.611	591.467	314.138	426.567	462.897	375.667	429.565	24.2809	12

Response variable=HPER Physostigmine Dosage=low

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	369.281	357.400	380.839	351.161	554.193	352.155	621.000	426.879	403.786	540.000	475.847	597.367	452.492	29.1800	12
15	392.821	396.143	379.893	344.000	417.043	359.720	561.227	412.706	433.036	550.800	530.964	594.040	447.699	25.0768	12
30	428.067	424.800	352.043	355.700	478.967	350.300	570.625	424.667	431.067	445.828	467.100	580.963	442.510	21.7983	12
45	358.481	419.375	371.308	349.833	492.773	562.000	564.500	460.625	362.300	437.875	434.679	526.185	444.994	22.4811	12
60	381.667	407.000	437.667	503.900	533.040	742.038	558.833	430.120	392.400	473.385	484.067	602.600	495.560	29.8229	12
75	422.733	415.636	424.300	359.500	511.767	357.643	579.800	413.133	348.767	476.933	490.321	541.577	445.176	21.6784	12
90	437.500	412.857	433.517	343.000	505.800	363.800	628.222	471.000	331.233	462.633	501.483	612.815	458.655	27.3211	12
105	443.929	423.600	434.214	321.900	512.467	370.160	764.333	475.433	310.625	477.276	514.828	535.444	465.351	34.3739	12
120	468.000	432.059	451.310	298.250	504.929	381.893	869.000	448.310	409.481	476.433	534.500	510.476	482.053	39.6676	12
135	477.393	413.933	455.241	299.000	503.400	353.818	586.500	448.586	352.300	487.533	557.893	475.478	450.923	24.4407	12
150	445.370	400.929	456.033	287.500	493.862	356.133	872.529	442.667	342.824	493.367	522.929	483.214	466.446	42.1699	12
165	413.600	403.444	480.714	308.357	471.885	356.333	686.800	417.357	.	494.333	543.759	478.400	459.544	30.3691	11
180	449.679	404.625	406.964	310.750	449.696	359.233	912.737	424.615	.	452.467	544.760	509.625	475.014	47.8604	11

Response variable=HPER Physostigmine Dosage=mid

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	356.565	364.065	336.564	362.576	475.042	378.255	505.333	429.51	458.382	504.281	542.000	483.844	433.035	20.4224	12
15	363.467	362.059	353.963	309.833	367.067	369.619	615.429	.	430.792	459.036	365.444	496.136	408.440	26.2032	11
30	418.115	363.933	340.862	310.250	423.964	429.133	598.500	475.00	384.467	350.481	406.000	501.357	416.839	22.9016	12
45	386.692	390.407	348.767	311.000	473.286	396.654	588.682	499.36	393.733	356.174	382.185	575.200	425.179	25.6780	12
60	373.875	411.783	398.414	317.000	530.931	410.833	685.857	500.25	416.100	337.545	416.067	485.724	440.365	28.7297	12
75	375.588	444.267	376.724	317.000	523.400	421.174	704.000	509.92	387.808	354.900	419.000	475.667	442.454	29.7467	12
90	379.400	430.708	372.467	343.000	504.655	391.923	899.250	1061.00	360.400	298.000	429.276	449.367	493.287	68.1687	12
105	398.500	409.750	416.034	357.071	524.241	407.250	611.800	509.00	353.767	315.000	432.033	458.111	432.713	23.8921	12
120	395.000	398.120	449.840	357.714	505.286	391.500	633.286	.	356.414	345.000	446.464	454.500	430.284	25.1985	11
135	413.474	389.429	406.160	378.688	517.862	401.692	636.882	472.57	363.000	352.000	430.172	427.241	432.431	22.8241	12
150	438.429	393.000	364.625	342.333	499.286	404.591	604.217	495.75	356.100	.	450.069	456.556	436.814	23.2728	11
165	420.000	.	372.808	.	494.567	413.034	653.211	498.78	338.821	372.852	449.207	470.261	448.354	28.3983	10
180	417.875	.	388.464	.	485.200	411.133	549.857	442.13	311.500	387.300	474.133	484.955	435.255	21.1727	10

Response variable=HPERVAR Physostigmine Dosage=ctrl

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	4.39434	2.56111	4.12105	4.14474	4.40000	4.03200	7.12414	4.54595	4.00545	5.53750	5.40204	6.15962	4.70233	0.343282	12
15	5.22222	6.20000	4.68750	4.13077	4.01176	4.62000	5.42500	4.38462	3.75000	6.00000	5.46154	6.34583	5.01994	0.255321	12
30	5.35000	6.10000	4.42333	3.92857	3.38500	4.99259	4.85000	5.32381	4.61000	6.24000	5.52667	6.58889	5.10991	0.273797	12
45	4.50417	6.20000	4.68333	4.61250	4.02941	4.34643	.	4.71429	4.24667	5.54615	5.66296	6.62778	5.01579	0.258305	11
60	5.41667	5.80000	4.74000	4.23750	4.42667	5.12333	5.90000	4.47391	4.34000	5.94815	5.00000	6.78889	5.18293	0.230718	12
75	5.60667	6.03333	5.18000	4.61000	4.20833	5.20588	5.33333	4.61111	4.32000	5.75556	5.46207	7.05909	5.28211	0.231650	12
90	5.81724	6.10000	4.98333	4.33750	4.77826	4.77000	7.11429	4.91481	3.93333	5.59310	5.42667	6.95517	5.39364	0.282460	12
105	5.91923	6.02000	4.99310	4.50000	4.93077	5.06667	.	4.30357	3.86333	5.39000	4.98571	6.81667	5.16264	0.253759	11
120	6.06522	5.94444	4.94000	4.35000	5.09000	5.42000	5.21667	4.66818	4.23448	5.40741	6.18000	6.49500	5.33428	0.210209	12
135	6.32667	5.66667	5.81250	3.81667	5.11429	4.61364	5.25000	4.95600	4.44333	5.24000	5.26333	5.25263	5.14631	0.189406	12
150	5.48667	5.62500	5.54000	3.86667	4.74348	3.97857	5.70000	4.60741	3.94667	5.59091	5.45000	5.42857	4.99699	0.209645	12
165	6.00333	6.01429	5.36429	4.14545	4.92273	4.93810	6.16667	4.38333	4.30000	5.56000	5.54667	6.86667	5.35096	0.242437	12
180	5.95333	5.90000	5.58667	4.01250	4.72857	4.65714	.	4.55556	4.41333	4.10000	5.02143	6.46364	5.03565	0.246978	11

Response variable=HPERVAR Physostigmine Dosage=high

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	3.70455	4.65185	4.28000	4.28800	5.54444	3.84444	5.40312	5.46296	4.96078	4.97455	4.85862	6.15490	4.84402	0.211369	12
15	4.63333	5.58750	3.63600	5.70000	4.52381	4.34643	6.95882	4.88929	5.24000	5.81250	4.63333	6.42083	5.19849	0.271520	12
30	3.00000	2.57500	3.25556	2.86087	6.05185	5.47308	6.33000	5.95000	4.56923	2.79444	4.39333	7.46667	4.56000	0.482108	12
45	2.43158	4.00000	3.56667	3.90000	6.11905	4.14667	6.00000	6.23667	3.76538	4.17500	3.93571	5.28929	4.46383	0.340928	12
60	3.06667	4.63571	3.67000	5.27667	5.78750	2.61875	6.30000	5.70000	4.58667	5.28333	4.33333	5.31667	4.71461	0.325726	12
75	3.60000	5.08148	4.42333	6.02414	5.89286	4.64333	6.93182	6.11000	4.46000	5.01000	5.36000	5.31667	5.23780	0.262266	12
90	5.00000	4.72500	4.80370	6.66522	5.94231	5.23000	6.91538	6.33077	4.72667	5.09655	5.77368	6.31667	5.62716	0.229687	12
105	3.81818	4.73333	5.21379	6.09231	5.92759	5.24000	6.90000	6.20667	4.52667	5.43333	6.35000	6.63000	5.58932	0.267059	12
120	5.25455	4.86364	5.29667	6.23158	5.69286	5.24000	6.84000	5.92000	4.96207	4.50000	6.13043	6.77667	5.64237	0.216585	12
135	5.84737	5.90952	5.14483	5.16667	5.82759	4.67000	6.93750	5.90345	4.25714	5.75294	5.83704	6.45333	5.64228	0.212118	12
150	6.41818	5.68947	5.65185	5.85000	5.81724	4.47667	6.97500	5.75000	4.13333	5.75000	6.13000	6.20333	5.73709	0.222891	12
165	5.77727	5.76000	5.78333	4.85833	5.61111	4.60333	6.93000	5.49333	3.96333	5.75667	5.73000	6.65000	5.57639	0.234042	12
180	6.02308	4.88571	5.86552	4.76923	5.63846	5.13333	6.83889	6.12000	3.51034	5.76667	5.55862	5.75667	5.48888	0.242257	12

Response variable=HPERVAR Physostigmine Dosage=low

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	4.41228	4.19500	4.46786	3.87419	6.51930	4.27931	8.90000	4.52241	4.14286	5.62857	5.30339	7.11429	5.27995	0.440053	12
15	4.94643	5.82857	4.96071	4.05000	5.26957	4.42000	6.35909	5.08824	4.70357	6.46000	5.90714	6.71200	5.39211	0.245964	12
30	5.51000	6.06000	4.99130	4.43000	5.98333	5.31667	6.61667	5.20000	4.78333	5.96897	6.22667	7.33333	5.70169	0.237667	12
45	4.50741	6.36250	5.05769	4.03333	5.94091	5.87037	6.73750	5.24583	4.93333	5.56667	6.12500	7.39630	5.64807	0.275962	12
60	5.01667	6.08750	5.70556	5.62000	6.38800	7.21923	6.93889	5.36000	4.72000	6.11154	5.96333	7.67333	6.06700	0.254240	12
75	5.66333	6.47273	5.55667	5.01000	6.26333	5.10714	7.03500	4.69667	4.59667	6.00333	5.95000	7.33077	5.80714	0.252957	12
90	6.21667	6.48571	5.51724	4.34545	6.27333	5.23000	8.08889	5.29667	3.44000	5.77333	5.71379	7.52963	5.82589	0.363507	12
105	5.83214	6.33000	5.71786	3.84000	5.94667	5.16000	8.77222	5.52000	2.77500	6.18966	5.80345	7.28333	5.76419	0.434857	12
120	6.42143	6.80000	5.64828	3.35000	5.92500	5.27500	8.25000	5.52414	4.76296	5.67667	5.54286	6.95714	5.84446	0.350903	12
135	6.70000	6.56000	5.59655	2.80000	5.90000	4.79091	7.50000	4.81379	3.96000	5.73667	5.69286	6.74348	5.56619	0.378945	12
150	6.28889	6.40000	5.79667	3.20000	5.78966	4.78333	8.13913	4.76667	3.81765	6.07667	5.87857	5.73214	5.55578	0.371661	12
165	5.75333	6.47778	5.69286	3.17143	5.90385	5.03000	7.56667	5.01786	.	6.13000	5.94138	6.00000	5.69865	0.327176	11
180	6.33571	6.33125	5.03214	4.05000	5.46087	4.93333	8.20000	5.20000	.	5.39000	5.62000	6.19167	5.70409	0.322774	11

Response variable=HPERVAR Physostigmine Dosage=mld

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	3.76522	5.20217	4.19636	3.56970	4.94375	4.05636	5.00714	4.52326	5.04909	4.82281	6.43929	6.08222	4.80478	0.249201	12
15	3.44000	5.00000	3.84074	2.44167	4.10667	5.09048	6.66429	.	4.92917	5.11071	4.63704	6.90000	4.74189	0.392252	11
30	3.38462	4.35333	4.25862	3.02500	5.82143	5.96667	6.79167	5.00000	5.45333	5.28889	5.93667	7.42857	5.22573	0.376889	12
45	2.70769	5.67037	4.41000	3.45455	5.98571	5.59615	6.63182	6.00909	4.55667	4.40870	5.30370	8.44000	5.26454	0.435898	12
60	3.28750	6.22174	4.99310	2.80000	6.49655	6.11333	6.79565	5.78750	5.19333	3.99091	5.80000	6.86897	5.36238	0.391209	12
75	4.67059	6.61333	5.23448	3.00000	6.51000	6.26522	7.60370	5.93077	4.81538	3.80000	5.76897	6.65833	5.57256	0.381130	12
90	4.83333	6.33750	5.27333	6.10000	6.23448	6.47692	8.58462	6.30000	5.15000	2.10000	5.64138	6.57000	5.80013	0.434954	12
105	5.52500	6.54500	5.63793	4.92857	6.57241	5.69583	7.41000	5.20000	4.56333	3.40000	5.79000	6.68148	5.66246	0.311586	12
120	5.43846	6.66400	5.71200	5.17143	6.22500	5.42143	7.67143	7.90556	4.66207	4.30000	6.01786	6.53667	5.97716	0.317400	12
135	5.92632	6.11429	5.58800	4.86250	6.49310	4.93846	7.62353	5.12857	4.69667	4.60000	5.90690	6.28621	5.68038	0.257769	12
150	6.27143	6.50000	5.11667	4.56667	6.22857	5.20000	7.47391	4.96250	4.00667	.	5.45172	6.35185	5.64818	0.303550	11
165	5.81786	.	5.43462	.	6.12667	5.61724	7.72857	4.95556	4.28571	4.68519	5.64483	7.02174	5.73180	0.328507	10
180	6.00833	.	5.80714	.	5.93000	5.60333	6.98571	5.20000	3.23462	5.12333	5.44333	7.18182	5.65176	0.345139	10

Response variable=VAGTONE Physostigmine Dosage=ctrl

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	1.35849	0.91667	1.26491	0.65000	1.43182	1.40400	5.97241	1.37838	1.63273	4.50000	3.98571	4.04615	2.37844	0.504440	12
15	1.94074	5.28667	0.98333	1.07692	1.28235	1.80400	5.70000	0.93462	1.51250	5.28148	4.15769	4.24583	2.85051	0.551132	12
30	2.17000	5.30000	2.21000	1.17857	0.24500	2.31852	3.86667	0.97143	2.09333	5.10000	3.73333	4.48519	2.80600	0.479625	12
45	2.01250	5.30000	1.71667	1.53750	1.81176	1.71071	.	0.61429	1.20667	4.05000	4.21481	4.57222	2.61338	0.480896	11
60	2.03333	4.87500	0.78667	1.32500	0.68000	1.70333	5.43333	0.83478	1.88333	4.27037	2.43000	4.33704	2.54935	0.495157	12
75	2.47333	5.11111	1.19667	0.48000	1.20833	2.12353	4.45000	0.36296	0.96000	4.14815	4.16207	4.68636	2.61354	0.516788	12
90	2.71034	4.65000	0.83000	0.53750	1.59130	2.75000	5.85714	0.07778	0.71333	3.80000	3.61000	4.60690	2.64452	0.547968	12
105	2.84615	4.52000	1.22414	0.36000	1.97308	2.57083	.	0.10000	0.64000	3.34667	2.72500	4.56111	2.26063	0.469964	11
120	3.22174	5.02222	1.48000	0.38333	2.21500	2.82333	4.06667	0.16818	1.12414	3.15926	4.90667	4.32500	2.74130	0.486425	12
135	3.69667	4.21667	1.61250	1.04444	2.06667	2.70455	4.20000	0.12800	1.89333	3.16333	3.32000	3.03158	2.58981	0.366158	12
150	3.00000	4.47500	1.87333	1.14667	2.23478	1.75714	6.30000	0.16296	1.10667	3.74545	3.05333	3.39524	2.68755	0.485212	12
165	3.29000	4.92857	1.77500	0.92727	1.94545	1.67143	4.96667	0.08333	1.01379	2.79333	3.79000	4.35000	2.62790	0.473743	12
180	3.47333	4.62000	2.01667	1.12500	2.69286	2.36190	.	0.06667	2.20667	2.29000	2.55714	4.29545	2.51870	0.391925	11

Response variable=VAGTONE Physostigmine Dosage=high

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	0.95000	2.64444	0.93400	0.87600	2.62593	1.21111	4.10937	1.74630	3.32549	3.66000	2.92241	3.58431	2.38245	0.343376	12
15	2.03333	4.25000	0.78800	0.00000	1.20952	1.83929	5.88235	0.98571	3.46000	3.76250	2.44444	3.56667	2.51849	0.491971	12
30	0.00000	0.30000	0.34444	0.14348	3.49630	0.53462	4.55500	1.32333	0.66923	0.35000	1.56667	4.35667	1.46998	0.487058	12
45	0.00000	1.44783	0.25000	0.97000	3.79048	0.86000	4.13000	1.38333	0.22692	0.88500	1.50714	2.88929	1.52833	0.395064	12
60	0.00000	2.25000	1.20667	2.05667	3.75417	0.00000	4.90000	1.84000	0.66333	0.88667	1.71852	3.53333	1.90078	0.439922	12
75	0.00000	3.02593	2.43667	2.54828	3.98571	0.28000	6.25455	2.87000	0.30000	1.64000	3.19000	4.10000	2.55259	0.525737	12
90	1.86000	1.75417	3.58519	2.58696	4.01923	1.15667	6.38462	2.67692	0.54333	2.27931	3.47368	4.56333	2.90695	0.464502	12
105	1.08182	2.50000	3.54138	2.03846	3.86552	1.01000	6.44667	2.67333	0.21667	2.57143	4.11923	4.84000	2.90871	0.509838	12
120	2.82273	2.66818	3.62667	2.28947	3.75357	0.99667	6.32000	2.71667	0.86552	3.03333	4.50000	4.94000	3.21107	0.450245	12
135	3.00000	3.88095	3.43448	2.05556	3.68621	0.48333	6.49375	2.62414	0.27143	2.94118	4.13704	4.77333	3.14845	0.497193	12
150	3.83636	3.54737	3.74444	1.85000	3.53103	0.41333	6.42500	2.44333	0.15000	3.22667	4.27000	4.53333	3.16424	0.505300	12
165	3.08182	3.65333	3.66667	2.05833	3.69259	0.80333	6.17000	2.28000	0.33667	3.19667	4.45667	4.60667	3.16690	0.469833	12
180	3.68077	3.17143	4.01724	2.32308	3.58846	0.94815	6.08889	2.23000	0.48276	3.52000	3.58621	4.16333	3.15003	0.432664	12

Response variable=VAGTONE Physostigmine Dosage=low

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	1.99474	2.79000	1.54107	0.92581	4.31404	1.64138	7.52500	0.10690	1.60893	4.47619	2.90847	4.73469	2.88060	0.595846	12
15	2.73214	4.84286	2.15000	0.81500	2.92609	1.25600	5.55909	1.07059	3.03571	5.11600	4.36786	4.14400	3.16794	0.473568	12
30	2.62000	5.12000	2.90000	0.38000	3.64667	1.77000	5.36250	0.95000	3.09000	2.68276	4.44000	4.74815	3.14251	0.462395	12
45	2.01481	4.90000	2.96154	1.31667	3.54545	2.50000	5.68125	1.71250	2.59000	2.85417	4.39643	4.83333	3.27551	0.402639	12
60	3.15667	4.52500	2.84444	2.35000	3.30800	3.45000	6.11667	1.90400	3.14667	3.95385	4.37000	4.69667	3.65183	0.332545	12
75	3.63333	4.69091	2.75333	2.37000	3.15333	2.20714	6.08000	0.31667	1.16667	4.07000	3.87500	4.51538	3.23598	0.460209	12
90	3.84667	4.97143	2.98621	1.50909	3.26667	2.32333	7.33333	0.69667	0.23667	3.80333	3.46552	5.34074	3.31497	0.578825	12
105	4.12143	5.06000	3.14643	0.79000	3.31000	2.49600	7.71667	0.93333	0.40000	3.99655	3.68966	4.46667	3.34389	0.591836	12
120	4.14643	5.47059	2.85862	0.00000	3.14286	2.45714	7.45000	1.26207	2.98519	3.77667	3.63571	4.62381	3.48409	0.553284	12
135	4.79286	5.57333	2.94828	0.00000	3.26000	2.20909	6.65000	0.60690	1.06667	4.03333	3.90357	3.88261	3.24389	0.579112	12
150	4.10000	5.19286	2.53667	0.00000	3.16897	2.10000	7.21739	0.47333	1.22353	4.21667	3.97143	3.21429	3.11793	0.588405	12
165	3.47667	5.04444	2.18214	0.10000	3.28462	1.84667	6.65333	0.33929	.	4.31667	3.99655	3.44400	3.15312	0.587670	11
180	3.75357	5.26875	2.20714	0.17500	3.13043	1.91000	7.06364	0.54231	.	3.47000	3.87600	3.75000	3.19517	0.597073	11

Response variable=VAGTONE Physostigmine Dosage=mid

TIME	CO2	CO4	CO6	N538	N584	N597	OLX	OL3	OPE324	OPE352	OPW	_005	_MEAN	_S_E	_N
0	1.07826	3.61957	1.66727	0.22424	2.26458	1.30909	2.68333	0.40698	3.51273	3.48421	5.45714	3.88667	2.46617	0.457955	12
15	1.08000	3.31176	0.74815	0.00000	1.44667	2.75714	5.49286	.	3.18333	3.38571	2.67778	5.34091	2.67494	0.532100	11
30	0.14231	1.53333	0.51034	0.00000	3.47857	2.29333	5.07500	1.40000	1.89000	1.96667	4.17000	5.43571	2.32461	0.531133	12
45	0.05385	3.45185	0.73000	0.10000	3.90357	1.98077	4.93182	2.81818	1.96333	1.21739	3.39259	5.90000	2.53695	0.538732	12
60	0.56250	4.72609	1.62414	0.00000	4.27586	2.75333	5.49130	2.75000	2.62000	0.10000	3.65333	4.66897	2.76879	0.542837	12
75	2.11765	5.56667	2.66897	0.00000	4.03333	3.36087	6.22963	2.24615	2.54615	0.07000	3.75517	4.52500	3.09330	0.552234	12
90	2.48000	5.36667	2.91333	0.70000	4.19310	3.44615	7.13846	3.20000	1.93667	0.00000	4.03448	4.59667	3.33379	0.566566	12
105	2.89500	5.58500	3.14828	1.02857	4.12414	3.15417	6.38000	2.20000	2.09000	0.00000	4.27000	4.46296	3.27818	0.526612	12
120	2.91538	5.45600	3.06000	1.04286	4.14286	2.87143	6.75238	3.90000	1.97931	1.40000	4.57143	4.26000	3.52930	0.479764	12
135	3.18421	4.75714	3.74800	1.55625	4.02069	2.98462	6.58824	1.41429	2.41667	2.10000	4.57586	3.78621	3.42768	0.428653	12
150	3.69048	4.30000	4.02083	0.86667	4.05714	2.96818	6.64783	2.02500	1.23333	.	3.98966	4.03704	3.43965	0.487904	11
165	3.35714	.	3.93077	.	3.85000	3.13448	6.63810	1.64444	1.43929	2.42222	3.99310	4.59565	3.50052	0.478476	10
180	3.52083	.	3.96429	.	3.85500	3.04333	5.93571	1.86667	0.23077	2.63000	3.59333	5.36818	3.40081	0.516357	10

APPENDIX R

ANOVAS FOR P-Q INTERVALS FOLLOWING PHYSOSTIGMINE SALICYLATE (EXPERIMENT IV), USING ALL ANIMALS, FOR THE FOUR EXPERIMENTAL WEEKS

NUMBER OF OBSERVATIONS IN DATA SET = 768

General Linear Models Procedures SAS

Dependent Variable: P-Q Interval

Source	DF	Sum of Squares	F-Value	PR > F
Model	381	0.057	3.57	0.0001
Error	316	0.013		
Corrected Total	697	0.070		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	0.015	43.52	0.0001
Animal*Dose (Group)	19	0.008	10.46	0.0001
Dose*Time	42	0.002	1.22	0.1710
Animal*Time (Group)	112	0.006	1.38	0.016

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	0.003	0.54	0.6679

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	0.0003	0.27	0.8443
Group*Dose	9	0.004	1.04	0.4467
Week	3	0.007	5.61	0.0063

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	14	0.0004	0.53	0.9090
Group*Time	42	0.002	0.70	0.9022

APPENDIX S

ANOVAS FOR PLASMA AND ERYTHROCYTE CHOLINESTERASE FOLLOWING PHYSOSTIGMINE SALICYLATE (EXPERIMENT IV), USING ALL ANIMALS, FOR THE FOUR EXPERIMENTAL WEEKS

NUMBER OF ANIMALS IN DATA SET = 144

General Linear Models Procedure SAS

Dependent Variable: Plasma Cholinesterase

Source	DF	Sum of Squares	F-Value	PR > F
Model	77	166.81	19.75	0.0001
Error	66	7.24		
Corrected Total	143	174.05		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	45.28	51.59	0.0001
Animal*Dose (Group)	24	5.63	2.14	0.0081
Animal*Time (Group)	16	6.20	3.53	0.0001
Dose*Time	6	-	29.03	0.0001

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	7.88	.46	.7152

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	33.05	46.99	.0001
Group*Dose	6	.59	.42	.8578
Week	3	6.97	9.92	.0001

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	2	41.65	53.73	0.0001

Dependent Variable: Erythrocyte Cholinesterase

Source	DF	Sum of Squares	F-Value	PR > F
Model	77	79.82	9.78	0.0001
Error	66	6.99		
Corrected Total	143	86.81		

Source	DF	Sum of Squares	F-Value	PR > F
Animal (Group)	8	15.43	18.20	0.0001
Animal*Dose (Group)	24	10.60	4.17	0.0001
Animal*Time (Group)	16	1.44	0.85	0.6278
Dose*Time	6	-	14.48	0.0001

Test of hypotheses using the MS for Animal (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Group	3	5.73	.99	.4450

Test of hypotheses using the MS for Animal*Dose (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Dose	3	12.24	9.24	.0003
Group*Dose	6	2.23	.84	.5510
Week	3	8.00	6.04	.0033

Test of hypotheses using the MS for Animal*Time (Group) as an error term.

Source	DF	Sum of Squares	F-Value	PR > F
Time	2	14.42	80.16	0.0001

APPENDIX T

MEAN PLASMA AND ERYTHROCYTE CHOLINESTERASE ACTIVITY
(EXPERIMENT IV)

Plasma Cholinesterase Activity (mM/l/min) for Monkeys Receiving

Four Physostigmine Salicylate Treatment Conditions

Animal #	Time (min)	Pyridostigmine Dosage (µg/kg) 0	25	50	100
C02	-30	3.061	2.862	3.040	3.124
	30	3.378	1.224	0.766	0.836
	180	3.382	1.789	2.422	1.452
C04	-30	4.152	4.289	4.151	3.797
	30	3.794	1.752	1.572	0.691
	180	4.796	2.719	1.852	1.262
C06	-30	1.220	1.227	1.624	0.946
	30	1.237	0.705	0.726	0.299
	180	1.855	1.043	1.158	0.635
N538	-30	2.385	2.695	2.621	2.771
	30	2.840	1.604	0.856	0.614
	180	2.865	2.133	1.414	0.919
N584	-30	2.085	2.606	2.507	2.618
	30	2.148	1.135	0.680	0.913
	180	2.159	1.778	1.050	1.182
N597	-30	1.589	2.296	1.295	1.566
	30	1.649	1.215	0.402	0.572
	180	1.721	1.815	1.099	0.889
OLX	-30	2.534	1.697	2.328	2.217
	30	3.017	0.964	0.932	0.532
	180	2.888	1.527	1.469	0.858
OL3	-30	2.743	1.757	2.058	2.508
	30	2.814	0.865	1.249	0.622
	180	3.144	1.599	1.193	0.917
OPE324	-30	3.295	2.725	4.290	4.446
	30	3.223	1.474	2.814	0.740
	180	3.610	2.567	3.144	1.139

Animal #	Time (min)	Pyridostigmine Dosage (µg/kg) 0	25	50	100
OPE352	-30	2.474	4.373	2.287	2.443
	30	2.335	1.277	0.797	0.679
	180	2.352	1.840	0.986	1.019
OPW	-30	3.910	4.048	3.667	4.454
	30	3.733	2.078	1.421	1.850
	180	4.096	3.030	3.109	2.654
005	-30	3.608	3.171	3.257	3.120
	30	3.493	0.690	1.398	0.626
	180	3.755	2.339	1.737	1.092

Grand Means (n = 12)

Time (min)	Pyridostigmine Dosage (µg/kg)			
	0	25	50	100
-30	2.755	2.812	2.760	2.834
(SEM)	(0.259)	(0.295)	(0.273)	(0.304)
30	2.805	1.249	1.134	0.748
(SEM)	(0.235)	(0.122)	(0.184)	(0.110)
180	3.052	2.015	1.719	1.168
(SEM)	(0.270)	(0.162)	(0.223)	(0.148)

Erythrocyte Cholinesterase Activity (mM/l/min) for Monkeys Receiving Four Physostigmine Salicylate Treatment Conditions

Animal #	Time (min)	Pyridostigmine Dosage (µg/kg) 0	25	50	100
C02	-30	2.786	2.276	2.356	3.049
	30	2.772	1.377	1.070	1.259
	180	3.233	2.355	2.160	2.358
C04	-30	3.160	4.222	2.275	3.645
	30	3.754	3.027	1.912	1.383
	180	3.217	4.234	2.604	2.843
C06	-30	3.115	2.409	3.297	2.490
	30	2.588	1.802	2.344	1.014
	180	3.645	2.261	3.018	1.905
N538	-30	2.710	2.517	3.595	3.053
	30	3.219	2.111	2.045	1.031
	180	3.496	2.681	2.867	1.532
N584	-30	2.402	2.657	2.228	3.901
	30	2.239	1.824	1.291	1.926
	180	2.141	2.116	2.048	2.575
N597	-30	3.118	3.578	2.371	3.336
	30	3.102	3.057	1.643	2.211
	180	3.233	3.678	2.791	2.030
OLX	-30	3.117	2.190	2.426	2.438
	30	3.211	1.552	1.659	1.735
	180	3.138	2.152	1.679	2.218
OL3	-30	2.544	2.713	1.447	2.066
	30	2.936	1.630	1.022	1.170
	180	2.850	2.337	1.296	1.541
OPE324	-30	2.338	2.486	2.705	3.363
	30	2.081	1.391	2.936	0.953
	180	1.957	2.230	2.850	2.066
OPE352	-30	2.806	3.720	3.323	3.115
	30	3.216	3.001	2.396	2.092
	180	3.910	3.449	2.834	3.288
OPW	-30	3.267	2.302	3.551	4.350
	30	4.179	2.204	1.822	2.453
	180	4.600	2.288	3.231	3.260

Animal #	Time (min)	Pyridostigmine Dosage (µg/kg) 0	25	50	100
005	-30	3.176	2.182	2.530	2.504
	30	2.697	1.774	1.756	1.024
	180	2.714	1.598	1.830	1.764

Grand Means (n = 12)

Time (min)	Pyridostigmine Dosage (µg/kg) 0	25	50	100
-30	2.878	2.771	2.675	3.109
(SEM)	(0.094)	(0.197)	(0.186)	(0.192)
30	3.000	2.063	1.825	1.521
(SEM)	(0.171)	(0.183)	(0.162)	(0.155)
180	3.178	2.615	2.432	2.282
(SEM)	(0.209)	(0.221)	(0.177)	(0.174)

* U. S. GOVERNMENT PRINTING OFFICE: 1990--761-051/20020 03-21-1990